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The carotid sinus mechanism and hypertension

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Dedicated to

my grandfather, N.L.

1880-1956

Dedicated to

My grandfather, M.L.

1880-1956

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INTRODUCTION:

There are many different theories concerning the pathogenesis of essential hypertension. The most important of these theories concern vascular sclerosis, humoral mechanisms, renal ischemia, hypoxia of the brain, and hypersensitivity of the vasoconstrictor centers.

Since the discovery of the aortic nerve by deCyon and Ludwig and of the carotid nerve by Hering, investigators have learned from numerous animal experiments that these nerves are most sensitive to minute changes in blood pressure. Physiologists Hering, Koch, and Heymans (19), (20) proposed, therefore, that essential hypertension may develop through disruption of the receptors of these nerves due to sclerosis of the arterial walls. Most of the later authors have denied the role of the sinoaortic regulatory system in the pathogenesis of essential hypertension because neurogenic hypertension, (44,c) which may be obtained by resection of the carotid and aortic nerves in animals, differs in its circulatory mechanism from essential hypertension.

Experiments by Koch, Heymans, and coworkers (21), (22) and Hauss and associates (16) have shown that arterial pressure does not act directly on the sino-aortic receptors, but indirectly by stretching the wall of the arteries where the receptors are located. Since it was known that the aortic and carotid sinus nerves provided a means of physiological regulation of the arterial blood pressure, it was suggested that the state of contraction, tone, tension, and distensibility of the arterial wall of the sino-aortic receptor areas could play a role in the mechanisms of reflex regulation and homeostasis of arterial blood pressure.

According to Pickering, (40) there is a good deal of evidence that the proprioceptive reflexes arising from the carotid sinus and the arch of the aorta are present in patients with hypertension; therefore, the study which follows was undertaken to shed some light upon the status of the carotid sinus mechanism in hypertension.

The first and most likely step seemed to be in finding a means whereby hypertension could be produced by manipulation of the carotid sinus area -- working on the supposition that the distensibility of the carotid sinus is the main determining factor in the so-called normal functioning of the carotid sinus mechanism and that alteration of this distensibility by rendering the vessels less-distensible should (and apparently does) alter the sinus regulatory mechanism in such a way that higher arterial pressures would be needed to produce the same degree of stretch on the muscular and elastic wall of the carotids which was previously accomplished by lesser pressures. All of this seems to indicate, as the remainder of my paper will attempt to bring out, that the carotid sinus mechanism is functioning in hypertension, functioning at a different -- a higher -- level.

REVIEW OF THE LITERATURE:

The constancy of the arterial pressure and of the other characteristics of the circulation appear to be due, at least in part, to proprioceptive reflexes from the vascular system. Of primary importance among these are the carotid sinus and aortic depressor reflexes. There is, in addition, considerable evidence suggesting that pressoreceptors are also present in the great veins and auricles on both sides of the heart, and possibly in the pulmonary arteries and their branches as well as in the left ventricle. There may as yet be others. (5), (13), (14), (17)

Although very little is known of the effects of stimulating these receptors -- except in the case of the carotid sinus and depressor nerves -- or of the part they play in the regulation of the circulation, present evidence suggests they may all act similarly in producing effects on the heart through the vagus and on the vessels through the sympathetic nerves.

Although less is known concerning their mechanism of action, the importance of chemo-receptors in the circulatory system is also recognized. The best known is the carotid body which is particulary sensitive to 0_2 lack and CO_2 tension, with reflex effects on respiration as well as circulation. Similar receptors exist in the aortic arch and probably elsewhere. Other receptors, responding particularly to amidines, exist in the coronary and pulmonary circulations.

Since my study is primarily concerned with the carotid sinus and the status of the carotid sinus reflex mechanism in primary essential hypertension, I shall endeavor to limit the following discussion to this area.

The histological picture of the wall of the carotid artery in the region of the carotid sinus differs from the usual picture of the large arteries (5), (20). This region shows a decrease in the muscle layer of the media, with replacement by elastic fibers and a thickened adventitia. The pressoreceptive nerve endings are located in the adventitia and media of the arterial wall of the carotid sinus and are connected with nerve fibers joining mainly the intercarotid branch of the glossopharyngeal nerve. Fibers have also been traced from the superior cervical ganglion and the nodose ganglion to the carotid sinus.

Electrical recording has shown that a burst of impulses ascends the carotid sinus and depressor nerves at each heart beat (6), (9). The electroneurogram of the dog's carotid sinus nerve reveals a train of potentials of various sizes forming compact volleys at each systole. All the larger and medium-sized potentials derive from pressoreceptor fibers. Apart from the larger potentials, there appears an electrical activity built up by axon potentials of very small spike heights in response to both chemical stimuli and intrasinusal pressure (10), (11).

Present evidence indicates that the large pressoreceptor spikes are elicited from stretch receptors acting in parallel with the contractile elements of the sinus wall. The pressoreceptors eliciting the small spikes do not act in parallel with these elements. They may be elicited from stretch receptors acting in series with the contractile elements. Another possible explanation is that they are elicited from nerve endings squeezed between the smooth muscle fibers in the media during distension of the wall as well as during active contraction of the muscle fibers (9), (10), (11), (28).

Furthermore, the effect on the peripheral blood pressure caused by a stimulation of the contractile elements in the sinus wall indicates the existence of a physiological mechanism which adjusts the sensibility of the blood pressure regulating mechanism in the carotid sinus region by changing the active tone in the sinus wall (25), (26).

The effects obtained from pressoreceptor units eliciting afferent spikes of different heights have been compared. Certain features, characteristic of the individual pressoreceptor have been observed. These properties are: the spike height; the absolute maximum frequency of discharge ($n_{max.}$); the maximum adapted frequency ($n_{a\ max.}$); and the threshold pressure of the steady discharge (28).

Landgren (28), (24) has shown that there is a certain pressure region within which the pressoreceptor records a pressure rise with an increased frequency of discharge. This region is called the recording range of the receptor. Its limits are defined. The recording range is characteristic for the individual pressoreceptor. For the large pressoreceptor fibers the recording range extends from 30-200 mm Hg with the threshold pressure of the steady discharge at 120-150 mm Hg. The comparison of $n_{max.}$ and $n_{a\ max.}$ values show that pressoreceptor fibers eliciting large spikes always display higher values for $n_{max.}$ and $n_{a\ max.}$ than those producing smaller spikes; i.e., the larger pressoreceptor fibers are always discharged at a higher frequency than the smaller when exposed to the same strength of stimulus. In spite of these differences between the different types of pressoreceptors their reactions to constant pressure and pressure changes are principally the same.

Above a certain level in pressure, the impulse frequency asymptotically adapts towards a steady discharge (n_a).

It has been stated that the rate of rise in the pressure is of decisive importance for the impulse discharge. The higher the $\frac{dp}{dt}$, the higher the impulse frequency will be, up to a certain limit. On the other hand, the adapted impulse frequency (n_a) during a constant pressure, is dependent only on the height of the intrasinusal pressure. The way in which the constant pressure level is reached is of no importance for the value of n_a.

In addition, it has been shown that for the pressoreceptors there is no critical slope of the pressure rise below which an impulse discharge cannot be elicited irrespective of the pressure height finally attained.

A minimum impulse discharge has been obtained between 50 and 60 mm Hg during pressure decreases to 0 mm Hg. An increased impulse activity was observed at pressure drops to 0 mm Hg. It is suggested that this increased impulse discharge is due to local deformations of the arterial wall at these low pressures.

The stimulation of the pressoreceptors of the carotid sinus apparently is a property of both the inherent elasticity of the sinus wall as well as the pressure of the blood against the wall (19), (20), (21), (25), (28).

In attempting to determine the extent to which each of these two factors influence the reflex, Hauss, Kreuziger and Asteroth (16) severed the nerve to the right carotid sinus and both depressor nerves (in the dog) leaving the left carotid intact and wrapped the left carotid

in different dogs with the following materials:

1. corset of gypsum (plaster of Paris);
2. silk fiber;
3. nitrocellulose dissolved in methyl or ethyl acetate; and
4. thin rolled, lead cuffs (2-7 mm in diameter).

With all of the above wrappings applied there was no reflex fall in pressure when the pressure in the carotid sinus was increased. With the removal of the wrappings the reflex was restored in all cases but one (nitrocellulose -- permanent damage?).

Any increase in pressure which did not alter the tension of the carotid sinus wall, no matter how great, did not call forth the reflex. Therefore, the initiation of the carotid sinus pressure reflex apparently is not directly dependent upon changes in the blood pressure per se, but rather upon the degree of tension to which the wall of the carotid sinus is subjected.

In addition, experiments by Koch, Heymans (19), (20), (21), (22) and co-workers have shown that arterial pressure does not act directly on the pressoreceptors, but indirectly by stretching the wall of the arteries where the pressoreceptors are located. It was suggested, thereupon, that the state of contraction, tone, tension, and distensibility of the arterial wall of the carotid sinus and aortic areas could play a role in the mechanisms of reflex regulation and homeostasis of arterial pressure.

This suggestion has been investigated by Heymans (20) in order to examine the influence on arterial pressure and on the reflex regulation

of blood pressure, of changes in tension, resistance to stretch and distensibility of the carotid sinus and aortic walls. For this purpose drugs known or supposed to contract or to relax the arteries were applied locally to the carotid sinus and aortic pressoreceptive areas. Heymans concluded from his experiments that the state of contraction and tension, and thus the resistance to stretch of the arterial wall where the pressoreceptors are located, are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure and the decrease of tone and resistance to stretch of the pressoreceptive areas could be a primary mechanism of hypertension.

In another investigation, Asteroth and Kreuziger (2) studied the effects of tension and stretching of the carotid sinus wall within twelve hours of death. The blood pressure measured during life and the internal pressure used in the experiment were correlated. These experiments confirmed the relationship between loss of elasticity in old age and the blood pressure values. In females this loss of elasticity sets in earlier than in males. It is most pronounced in essential hypertension, and especially in malignant hypertension. In hypertension with nephritis, however, there were only changes compatible with age, in no way differing from those in people with normal blood pressure.

Furthermore, Donzelot, Meyer-Heine, Kolory and Chartrain (8) found that the carotid piezograms of 124 hypertensives (not further defined) showed practically constant modifications. The clinical course of the

affection apparently runs parallel with the carotid piezographic appearances and they conclude that the gravity of the condition appears to be less a function of the blood pressure level than of the arterial involvement shown by the piezogram.

In a recent clinical study Kezdi (25) raised the following provocative question: "---why is the elevation of blood pressure in hypertension not counteracted by the depressor reflex which is initiated by the carotid sinus and aortic nerves?" To shed further light on this point Kezdi employed a procaine block on the carotid sinus nerve and found, somewhat surprisingly, that the reaction elicited was identical in normal persons and in hypertensive patients (essential, malignant, and nephritic). This raised yet another question -- "how can the carotid sinus have the same reaction to procaine block in normal and in hypertensive patients when the starting level of the blood pressure is so different?" Since this is so, Kezdi believes the observations may be explained by assuming that the carotid sinus must be under the same degree of stimulation in hypertension and in the normal state, from which he further concluded that there must be a loss in arterial wall elasticity in hypertension.

In attempting to answer his first question, Kezdi's explanation runs as follows: the receptors of the carotid and aortic nerves perceive the elevated blood pressure in hypertension as being normal because the elevated blood pressure causes the same degree of stimulation to the carotid and aortic nerve receptors as the normal blood pressure in normotension.

The clinico-pathological aspects of carotid sinus function and hypertension have never really adequately been explored owing undoubtedly to the apparent neglect so commonly afforded the cervical regions in the routine autopsy.

Fisher (12) in 1951 noted that in spite of the fact that in the past the cervical portion of the internal carotid artery had apparently been examined completely only once or twice at autopsy, there was fairly good agreement that atherosclerotic change in the region of the carotid sinus is the pathological basis of thrombosis of the internal carotid artery.

It has been known for many years that the first portion of the internal carotid artery is especially liable to atherosclerosis. In one study it was found that the intensity of the atherosclerotic change was second only to that in the abdominal aorta. Chiari(12), after examining the carotid vessels in 400 cases, concluded that the internal carotid artery was affected just as severely as the abdominal aorta.

Following the discovery of the physiological importance of the carotid sinus mechanism in the regulation of the systemic arterial blood pressure several studies were undertaken to determine the possible relationship between pathological changes in the carotid sinus and hypertension. The chief concern of these studies was to find evidence that atherosclerotic change had destroyed the nerve endings in the carotid sinus. The question of elasticity, tonicity, and distensibility were not considered and therefore, in the light of subsequent knowledge the conclusions of these early studies may not be entirely valid or correct and must be judged accordingly.

Keele (24) examined fifty-five consecutive unselected cases, studying the condition of the carotid sinus and noting any relationship to hypertension. Atheromatous changes were of very frequent occurrence in the carotid sinus and were noted in fifty of the fifty-five cases examined. The lower part of the sinus was more markedly affected than the upper. The bifurcation angle was also frequently involved. The common carotid artery was involved less frequently than the sinuses, and showed the most definite changes in its upper part just below the point of bifurcation.

Among the eighteen cases in Keele's study with marked sinus involvement there were only two instances of hypertension (no definition provided). The remaining sixteen cases showed normal blood pressure and heart weight and could not reasonably be regarded as instances of hypertension. Among the thirty-two cases with slight involvement of the carotid sinus there were four instances of hypertension.

Keele concluded that no relationship could be established in his series between the degree of sinus involvement and the presence of hypertension.

Although Keele and Hasselbach (15), who made a similar study, both were unable to show any relationship between atheromatous changes in the carotid sinus and hypertension, a more fruitful approach might have been made in attempting to display a relationship between atheromatous changes and arterial wall distensibility, for as the later work of Heymans (21) and others has shown, the state of function of the carotid sinus mechanism is most intimately concerned with the tonic state

of the arterial wall. Another possible conclusion which may be reached in retrospect is that the work of Keele and Hasselbach indicates that atheromatous change, per se, does not alter the distensibility of the vessel so effected; however, this does not appear to be really the case. Whatever conclusions can be drawn, it seems obvious that further investigations along these lines, i.e., atheromatous changes versus elastic changes and the etiology of hypertension, are certainly indicated.

Wakerlin and his associates (45), (46), (47) on the other hand have also been interested in the role played by the carotid sinus mechanism in hypertension and have attacked the problem from a similar approach but with a different hypothesis. Rather than rendering the vessels less-distensible, per se, he has proceeded in a series of experiments with dogs to constrict the sinuses by means of in vivo plastic clamps. He found that bilateral constriction of the carotid sinus area by a plastic clamp with reduction of the palpable pulse of the sinus and internal carotid artery to one-third its former volume, produced a significant, sustained increase in the arterial blood pressure in nine of ten dogs. The onset of hypertension was rapid in four animals, gradual in five.

Since this initial work, Wakerlin has also succeeded in producing hypertension in dogs by the following manipulations:

1. bilateral constriction of internal and external carotids above the sinus in 2 of 2 dogs.
2. bilateral constriction of the denervated sinus in 1 of 1 dog.

3. bilateral removal of the carotid sinus in 3 of 4 dogs.

4. bilateral vertebral artery constriction in 1 of 3 dogs.

It should be noted and emphasized that the vessels were constricted so that the palpable pulse was decreased to one-third its normal value. It is on this basis that Wakerlin believes the pathogenesis of the hypertension thus produced involves an alteration in cerebral hemodynamics with both increased vasoconstrictor nerve tonus and a possible humoral factor.

What effect Wakerlin's manipulations may have had on the pressoreceptor mechanism of the carotid sinus is difficult to evaluate because no attempt was made to study any alterations in impulse discharge at varying intrasinusal pressures to determine the status of the mechanism; however, the fact that he resorted to actually constricting the vessels and not merely altering their distensibility and the fact that similar results were obtained when areas presumably not a part of any pressoreceptor mechanism were constricted and produced identical results -- hypertension -- it seems quite plausible that Wakerlin's hypothesis for the pathogenesis of the hypertension, i.e., altered cerebral hemodynamics, is yet another form of hypertension probably related but not identical to that hypothetical class in which altered sinus tonicity and distensibility in itself may produce hypertension. It is this last point with which I am particularly concerned.

From the findings already described, I have developed the following working hypothesis, namely, that since the state of the tone of the arterial wall apparently determines the state of function of the carotid

sinus reflex mechanism, a method which would render the carotid sinus less distensible should result in an elevated arterial blood pressure, the extent of which would depend upon two factors:

1. the degree to which the carotid sinus mechanism is concerned in the regulation of the arterial blood pressure, and
2. the degree to which the carotid sinus can be rendered less-distensible.

Since many workers have demonstrated the role of the carotid sinus reflex in arterial blood pressure regulation and yet others (25), (27) have shown that the mechanism is intact in hypertension -- essential as well as nephritic -- it would seem to follow that any increase in the arterial blood pressure which may result from attempts to render the sinus wall less distensible without actually constricting the vessel wall would lend support to the evidence of those workers who believe that primary, essential hypertension is a disorder of the vascular system in which the tone of the arterial wall is altered in such a manner as to render the wall less-distensible, less elastic. The mechanism of this hypertension might then be described as follows: a decrease in arterial wall distensibility requires an increase in arterial blood pressure to produce the same degree of arterial wall stretch that a previously lower arterial pressure was capable of producing. Since it has been demonstrated that the carotid sinus reflex is initiated by the stimulation of stretch receptors in the arterial wall, an increase in arterial blood pressure will now be necessary to produce the same degree of stimulation

of these receptors as before. The carotid sinus reflex mechanism will then apparently be shifted to a higher base-line with the result being a state of hypertension which in its earliest stages should be wholly dependent upon the degree of alteration of the tonicity of the arterial wall. In its later stages renal and endocrine mechanisms will undoubtedly enter into the overall picture.

From these preceeding studies it seemed to me that the next step to be taken along these lines would be to render the carotid vessels permanently non-distensible or as nearly so as possible with the anticipation that such a procedure might produce a state of hypertension similar to the clinical entity known as essential hypertension.

MATERIAL AND METHODS

To test this hypothesis six, young male dogs (mongrels), averaging twelve kilograms in weight, were obtained during the summer of 1955, and a similar group of ten male dogs during the summer of 1956. Since the experiment would entail pressure readings over an extended period of time, I decided upon using an auscultatory method for estimating the blood pressure as described by Allen (1).

The only essential equipment required is an ordinary sphygmomanometer, a cuff of the size used for infants and a stethoscope with a small diaphragm-piece. The blood pressure can be taken in any position of the animal, but the most convenient routine has been to have the dog standing up. The lower part of the hind leg, which has previously been cleanly shaven, is palpated for the course of the femoral artery, which ordinarily can be easily traced to the inner and anterior aspect of the limb above the ankle joint (if more advantageous, one of the fore limbs may be used). The stethoscope diaphragm is applied to the artery. The cuff is then wound around this part of the leg, including the diaphragm when practicable. Blood pressure readings are then obtained in the usual manner; however, the point of sudden diminution in sound is used for diastolic pressure determinations rather than the point of disappearance of sound.

Estimations of blood pressure by use of this method have shown a satisfactory parallelism with readings of a mercury manometer connected directly with the carotid artery according to Allen. Average values obtained with quiet, unanesthetized dogs were as follows:

systolic pressure	139 mm Hg.
diastolic pressure	79 mm Hg.
pulse pressure	60 mm Hg.

Employing the method just described, I obtained values somewhat higher than those of Allen. Daily readings on the six male dogs of the first summer gave the following averages:

systolic pressure	150 mm Hg.
diastolic pressure	90 mm Hg.
pulse pressure	60 mm Hg.

Although the animals were apparently quiet and relaxed while their pressures were being obtained, environmental conditions were far from ideal -- temperatures ranged from 90° to 100° F and the humidity readings were above 75%.

Since the diastolic reading required a judgement of sudden diminished sound intensity and because of the intolerable working conditions, I decided to record only changes in systolic pressure. To further facilitate matters the auscultatory method was abandoned and pressure readings were determined by the palpatory method. Average readings obtained by this new method differed only slightly from those obtained by the auscultatory method. They were as follows:

systolic pressure (by palpation)	154 mm Hg.
systolic pressure (by auscultation)	150 mm Hg.

After accumulating pressure readings to serve as base lines for the future experimentation, the next step entailed finding a suitable material for rendering the carotid arteries less distensible. Various

wrappings as used in cardiovascular surgery for reinforcing aneurysms were studied (42). The most popular of these was the use of dry diacetyl phosphate impregnated on polyethylene film and rendered sterile by soaking in Zephirin. The great drawback with this material as with many other wrappings is the fibrotic reaction which they stimulate -- a desirable end in cardiovascular surgery, but one which was undesirable for my purposes.

A new non-reactive nylon mesh was mentioned in a paper by Poppe (42); however, it was still uncertain just what properties this mesh might manifest in vivo. The E. I. duPont Company was kind enough to supply me with various samples of their new polyester films, including "Mylar"; however, because no one had reported using this material in vivo before, I hesitated to use the film on my small and limited supply of animals and finally decided to use a plastic solution described earlier by Rau (43). He employed this particular solution in a study of renal hypertension where he substituted the plastic for the sterile cellophane used by Page (36) to produce hypertension in his work on cellophane perinephritis. The solution consisted of butyl methacrylate polymer dissolved in acetone (200-250 ml. per 100 grams plastic).

According to Rau this plastic solution hardens quickly into a tough capsule which is not disturbed by body fluids, body temperature, or movements of the animal. He used a large atomizer to spray the plastic and also noted that toluene could substitute for acetone as the solvent.

A diagram of the anatomy of the region involved in my experimentation is presented in order to clarify certain differences and to em-

phasize similarities between the dog and man. The most significant difference lies in the fact that the dog's common carotid arteries trifurcate into internal carotid, external carotid, and occipital artery in distinction to the usual bifurcation into internal and external carotid arteries in man. See diagram in appendix.

The operative procedure itself is relatively simple, involving primarily the exposure of both carotid sinuses and their associated innervation. The operative procedure is as follows: the dog is given 0.8 cc Na nembutal (5% solution)/kilogram body weight intraperitoneally. Full anaesthesia usually follows within fifteen minutes. If the degree of anaesthesia is not sufficiently deep, a small dosage of sodium nembutal intravenously will produce the desired results.

A rubber intratracheal tube approximately 1.2 cm. in diameter is then inserted upon inspiration. The animal is next placed on its back and its neck is cleanly shaved with a straight blade. All four limbs are firmly secured. An area from the animal's chin to his sternal notch is thoroughly cleansed and prepared for surgery. Sterile precautions are exercised throughout.

A mid-line skin incision is made. The sternomastoid muscle is cleaved from the underlying muscles and fascia with the fingers or with a blunt instrument. The common carotid lies in a sheath with the vagus nerve and the internal jugular vein just beneath the sternomastoid and sternohyoid muscles and between the medial border of the sternomastoid and lateral border of the sternothyroid. Each common carotid tirfurcates at the level of the thyroid cartilage into vessels of unequal

size. The carotid sinus is intimately associated with the site of trifurcation and frequently extends a short distance up the internal carotid. A slight hazard to be avoided, in addition to the numerous veins in this area, is the hypoglossal nerve which in its course through the upper neck passes very close to the carotid sinus, and its associated fascial covering is often found to be somewhat adherent to the carotid sheath from which it can usually be easily dissected free.

With the carotid sinus clearly exposed bilaterally and with the nerves to the sinus safely identified, the area is wiped dry with cotton balls. The solution of butyl-methacrylate polymer dissolved in acetone is then slowly poured over the surface of the common carotid and the three vessels which take origin from it -- internal carotid, external carotid, and occipital arteries -- making sure to include the entire carotid sinus and being as careful as possible in avoiding the nerve to the sinus. With the aid of an atomizer, a stream of air is then played over the area to which the plastic solution has just been applied and in a matter of seconds the solution hardens, rendering the vessel wall less-distensible as witnessed by the decreased pulsations of the arterial wall with each heart beat. There is apparently no constriction of the vessel wall involved in this procedure.

The carotid sheath is not reapproximated. Muscles and fascia are reapproximated with sterile silk sutures. The skin incision is closed and covered with a sterile gauze square soaked in Zephirin and saline. Crystalline penicillin (sodium, G) 200,000 units are given intramuscularly immediately postoperatively. A similar dose is given

during the next 24 hours and a third dose is administered when and if indicated. A simpler procedure, in which the plastic solution was injected directly into the carotid sheath, was tried on four animals with rather poor results -- two dogs dying immediately.

The animal is not fed the day of operation and is given small amounts of ground meat the day following and is returned to a diet of regular lab chow thereafter. The stitches are removed five to seven days postoperatively.

RESULTS:

The procedure as stated above was carried out on three dogs during the summer of 1955. One dog never regained consciousness and died several hours postoperatively. A second dog regained consciousness following the operation, but fell into a coma the following morning and died shortly thereafter approximately 24 hours postoperatively. The third dog survived the procedure, but his postoperative recovery period was noteworthy in that the animal developed an abscess in the neck at the lower end of the closed skin incision. This animal was treated vigorously with penicillin and Terramycin and on the seventh postoperative day the abscess ruptured spontaneously, draining freely for two days after which the site gradually healed and the dog proceeded to make an uneventful recovery.

The first two animals were examined after death for any clues to their demise. As far as could be determined grossly, there were no hemorrhages at the operative site and the carotid vessels were neither occluded nor thrombosed. Both animals' lungs were congested and there were numerous small hemorrhagic foci the nature and cause of which could not be determined. Although the cause of death was not determined in either animal, I felt certain that the operative procedure per se was not the cause but probably the precipitating factor in some underlying pathology.

During the summer of 1956 additional dogs were obtained. One died before the experiment was underway, while two other dogs died immediately post-operatively. Another animal died twelve days post-operatively and

yet another approximately five weeks following surgery. The remaining five dogs recovered from the operative procedure and lived for periods ranging from two to four months, and were sacrificed at varying times in attempts at evaluating the functioning of the nerve to the carotid sinus. The one animal which survived the experimental procedure during the summer of 1955 lived through until the early summer of 1956, at which time it was sacrificed -- ten months post-operatively.

The functional status of the carotid sinus nerve in the experimental group which became hypertensive was evaluated by low voltage electrical stimulation to the nerve, which resulted in a fall in blood pressure in each animal so tested (#4, #7, #16) and which indicates that the nerve was intact.

The results are summarized in tabular form as well as graphically in the appendix. See Tables I and II and Graphs #1 - #16. Several photomicrographs are also included in the appendix.

SUMMARY:

The object of my study was to shed some light on the status of the carotid sinus mechanism in hypertension. To accomplish this end, a method of producing hypertension solely by manipulation of the carotid sinus region was devised.

The method employed was a relatively simple one, involving the coating of the carotid vessel walls of a group of dogs with a butyl methacrylate polymer-acetone preparation. The method was based upon the premise that the rate at which the carotid sinus nerve fires is dependent upon the degree to which the carotid sinus wall is stretched. By rendering the carotid sinus wall less-distensible, I hoped to alter the carotid sinus reflex mechanism in such a way as to make the intrasinusal pressure necessary to set off the reflex pitched at a higher level.

Of ten dogs in the experimental group, six lived long enough following surgery to provide sufficient data for evaluation. Of this group, four dogs became and remained hypertensive. The other two dogs remained normotensive. A hypertensive dog was defined as one whose systolic blood pressure as determined by palpation was elevated from its normal base-line by at least 35 mm Hg for at least six weeks. Each dog in the control group remained normotensive.

Although my series does not include a large enough number of animals for statistical analyses, I feel that my work has been fruitful in that I have succeeded in producing hypertension and thereby, I believe, lent some additional emphasis to the fundamental role of the biologic

condition of the carotid sinus wall in the reflex regulation of blood pressure, and have indirectly demonstrated a possible etiology of hypertension in man.

APPENDIX

TABLE I

Total Number of Dogs (Male 9-15 kg.)	16
Dead before Surgery (or lost for other reasons)	4
Controls	2
Experimental	10
Controls - 2	
Hypertensive	0
Non-hypertensive	2*
* one died twelve days post-op	
Experimental - 10	
Hypertensive	4
Non-hypertensive	2
Dead immediately or shortly post-op	4

Note: A hypertensive dog was defined as one whose systolic blood pressure as determined by palpation was elevated from its normal base-line by at least 35 mm Hg for at least six weeks.

TABLE II

Animal (all male dogs)	Weight (kg.)	Comments
#1	14.9	dead before surgery
#2	10.9	experimental; dead 24 hours after surgery
#3	14.1	dead before surgery
#4	11.8	experimental -- hypertensive
#5	10.9	experimental; dead after surgery
#6	11.1	lost to experiment -- used by someone else for another experiment
#7	9.7	experimental -- hypertensive
#8	9.7	control -- normotensive
#9	9.8	experimental -- normotensive
#10	12.2	experimental; dead immediately after surgery
#11	10.2	experimental -- hypertensive
#12	11.5	experimental; dead immediately after surgery
#13	12.1	experimental -- normotensive
#14	12.6	control -- normotensive; dead two weeks after surgery -- large peritracheal abscess
#15	11.8	dead before surgery
#16	12.1	experimental -- hypertensive

NOTE:

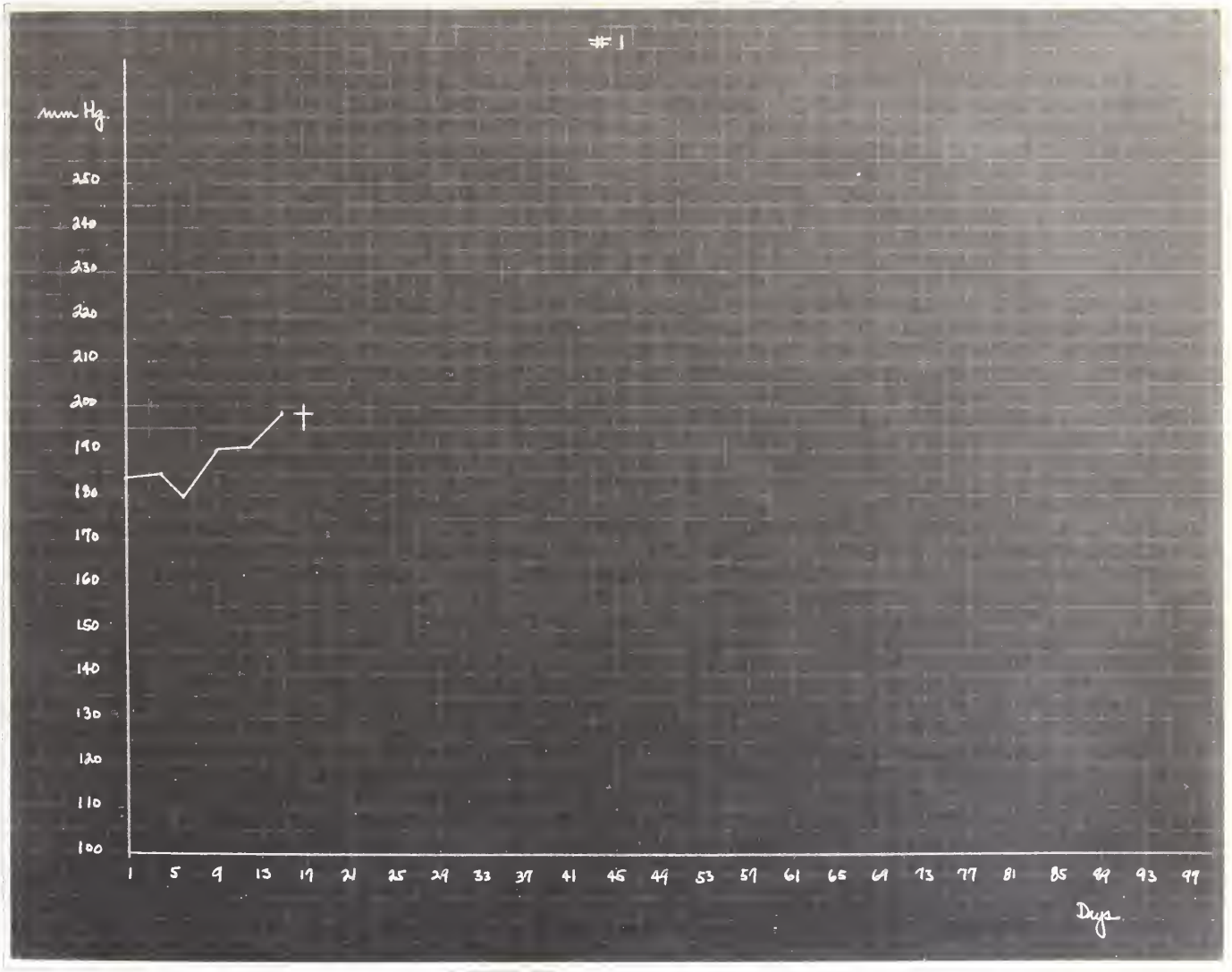
These comments are made in regard to the graphs which follow.

1. Numbers on each graph refer to animal numbers as in Table II.

2. Mm. Hg represents systolic pressure recording.

3. Vertical lines indicate the day on which the operative procedure was carried out.

4. Crosses (†) indicate the day the animal died or was sacrificed.


#1
mm Hg.
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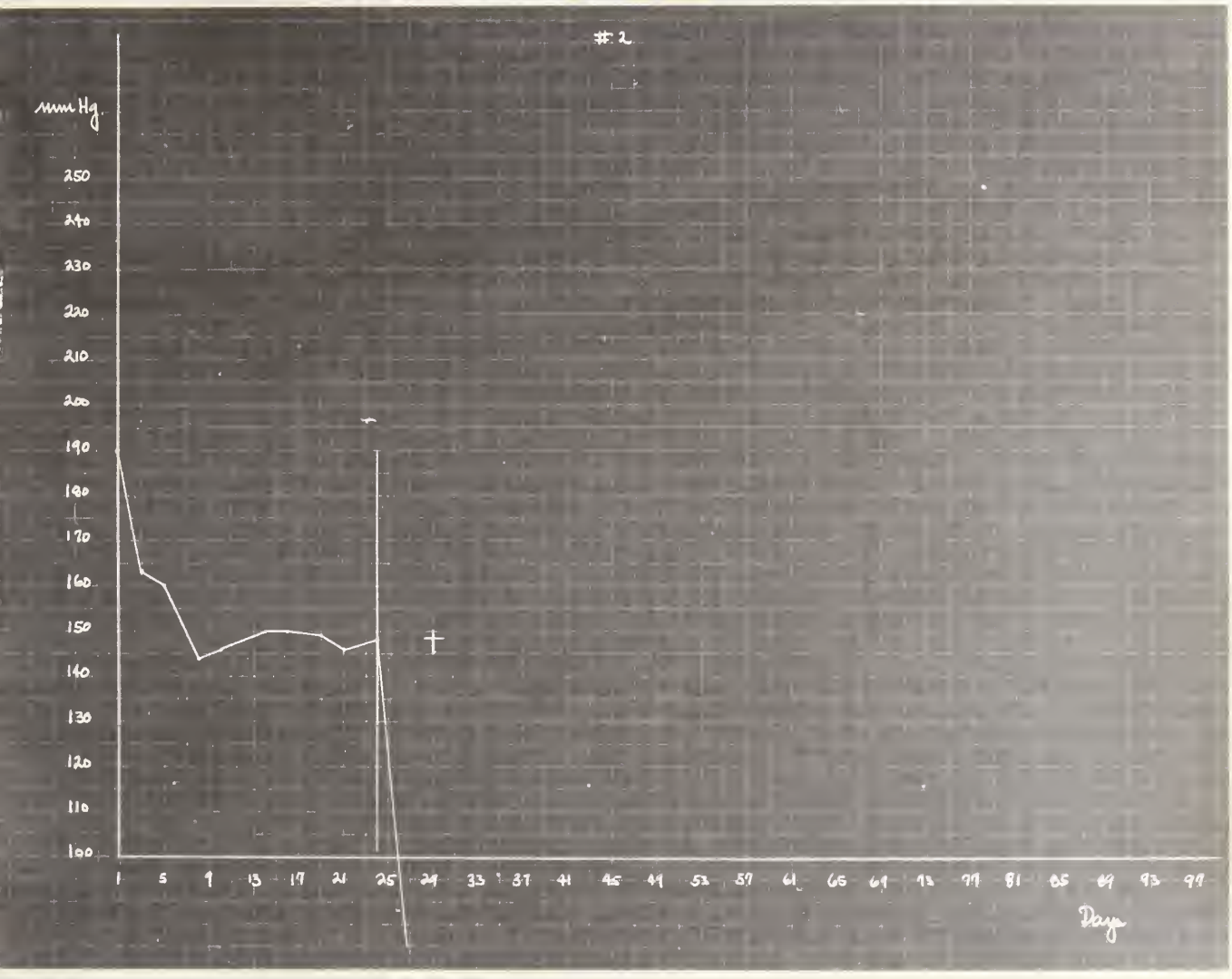
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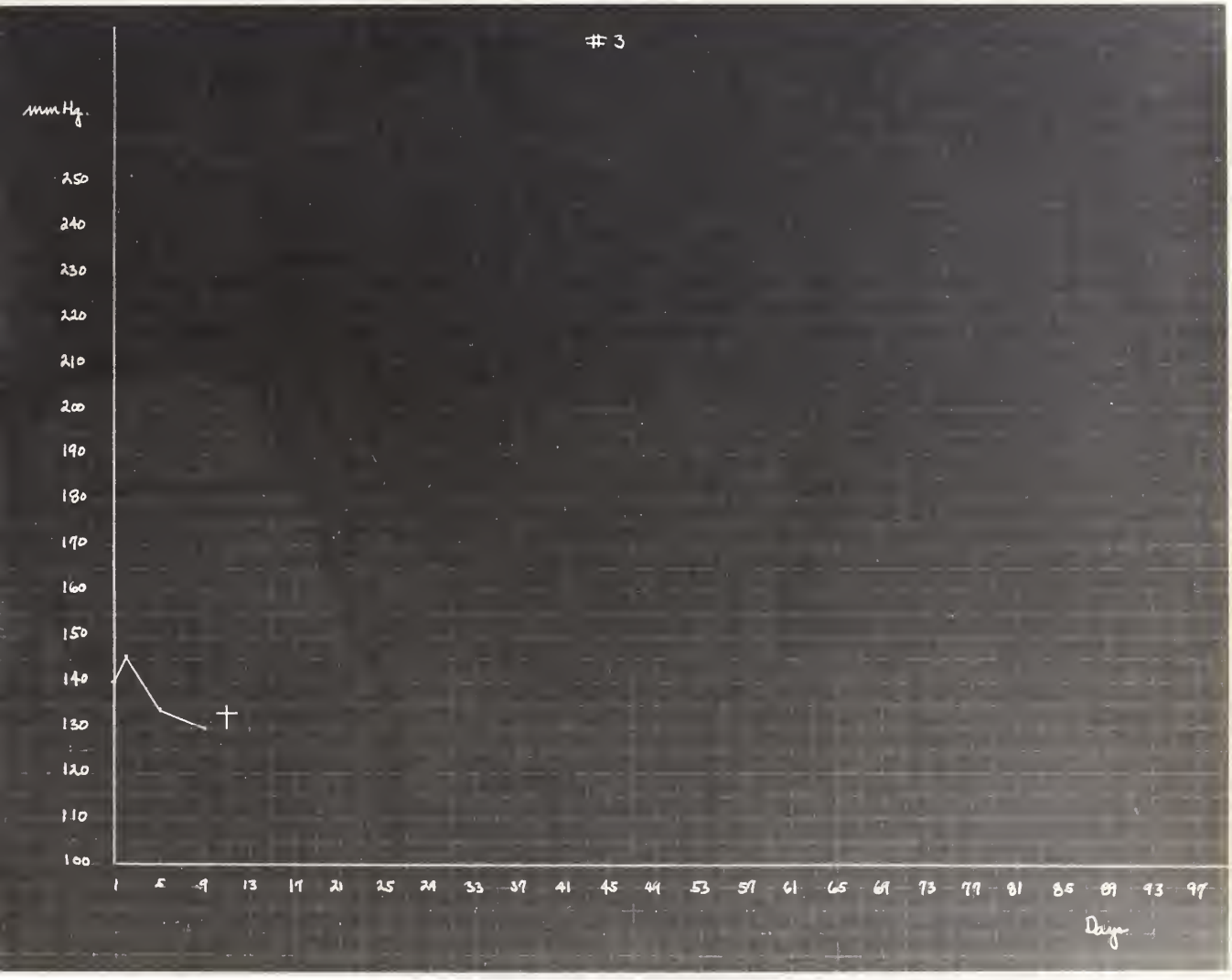
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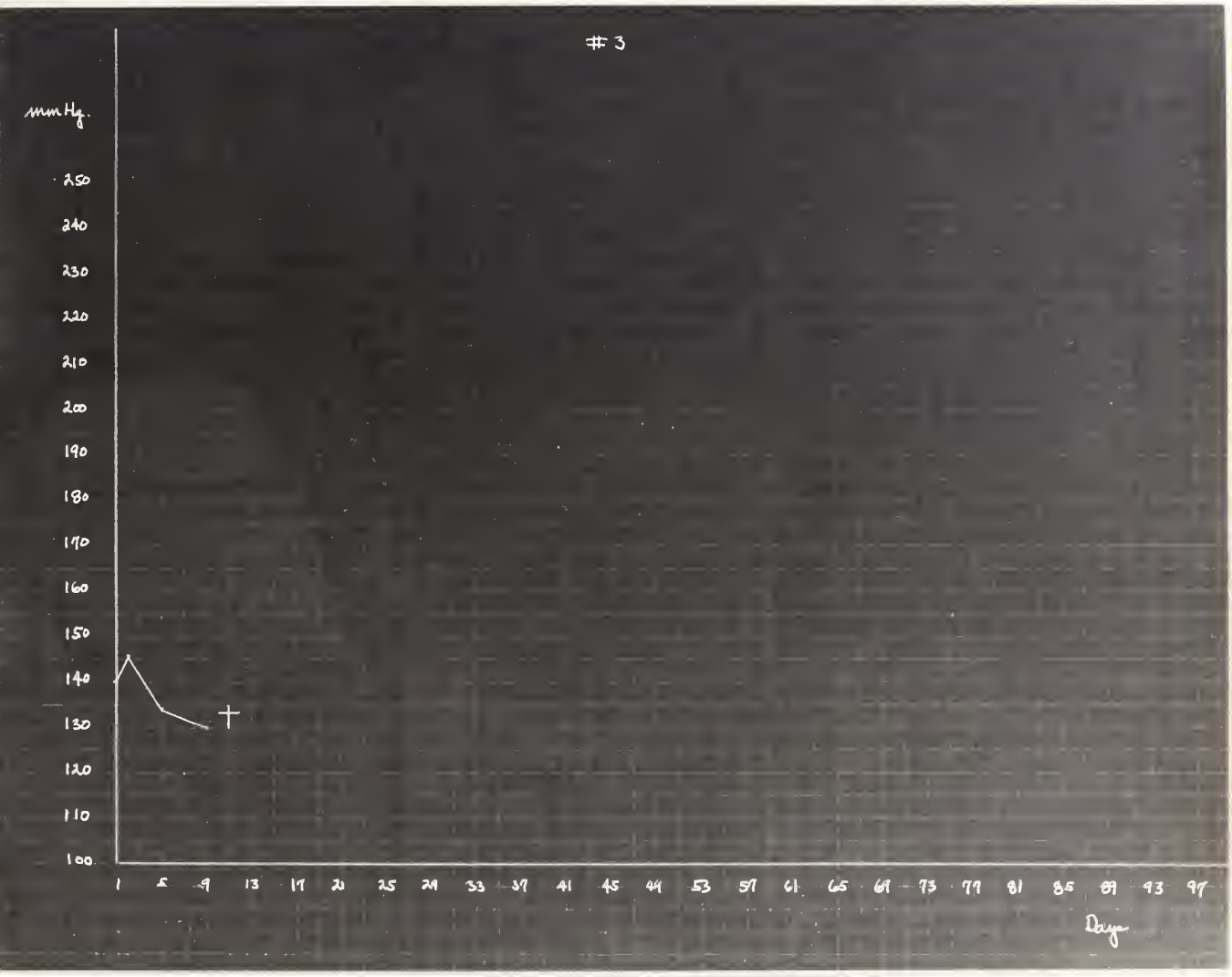
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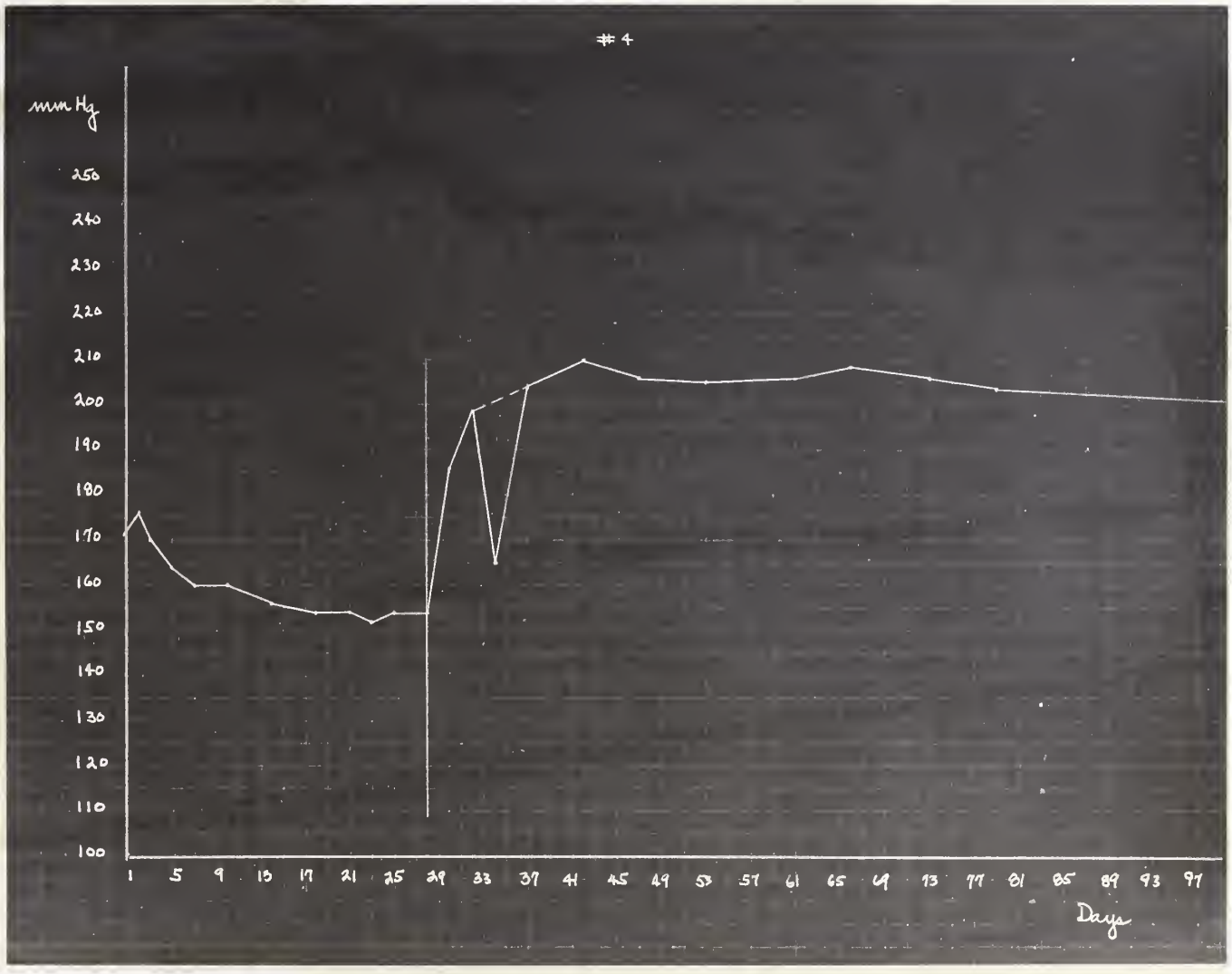
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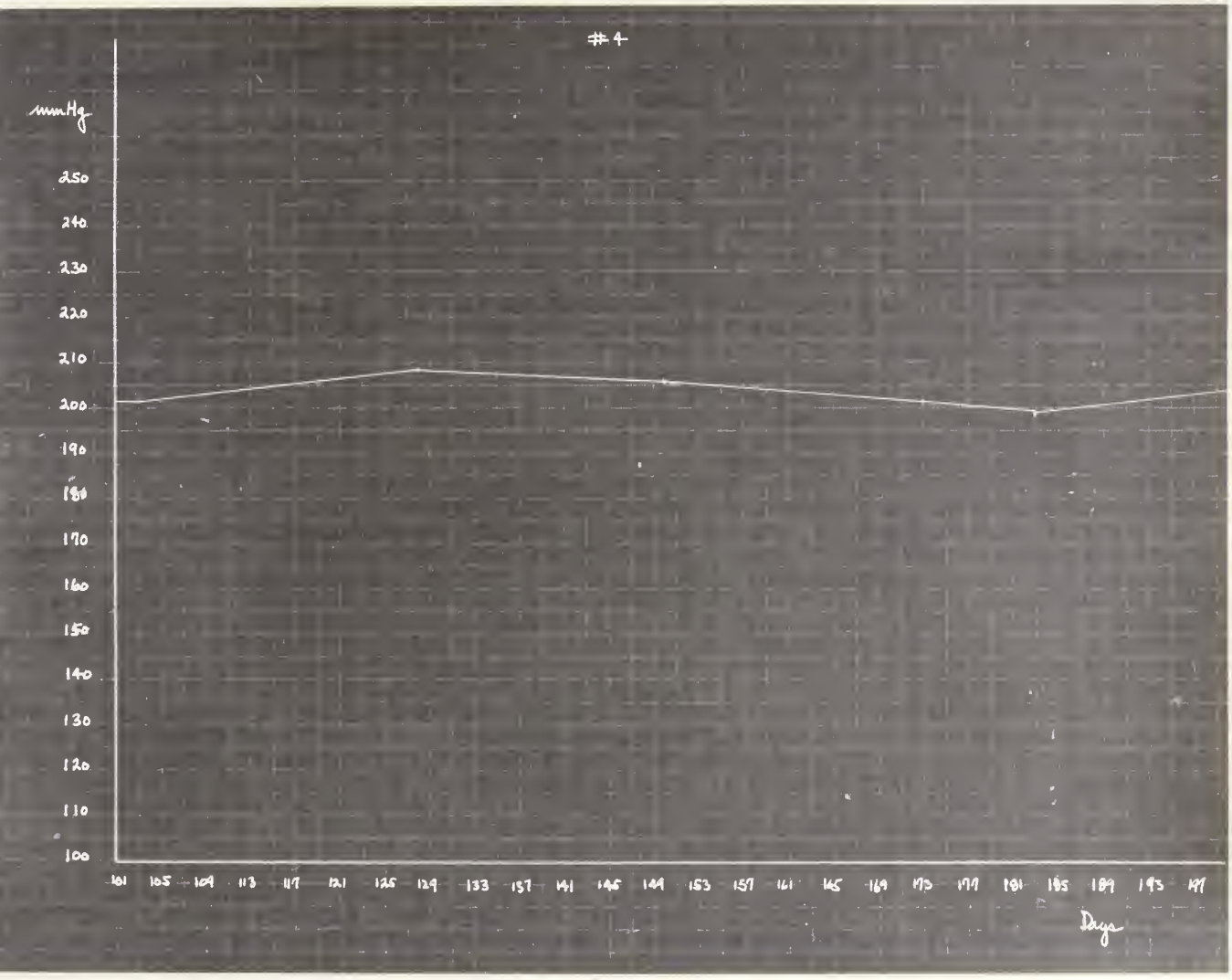
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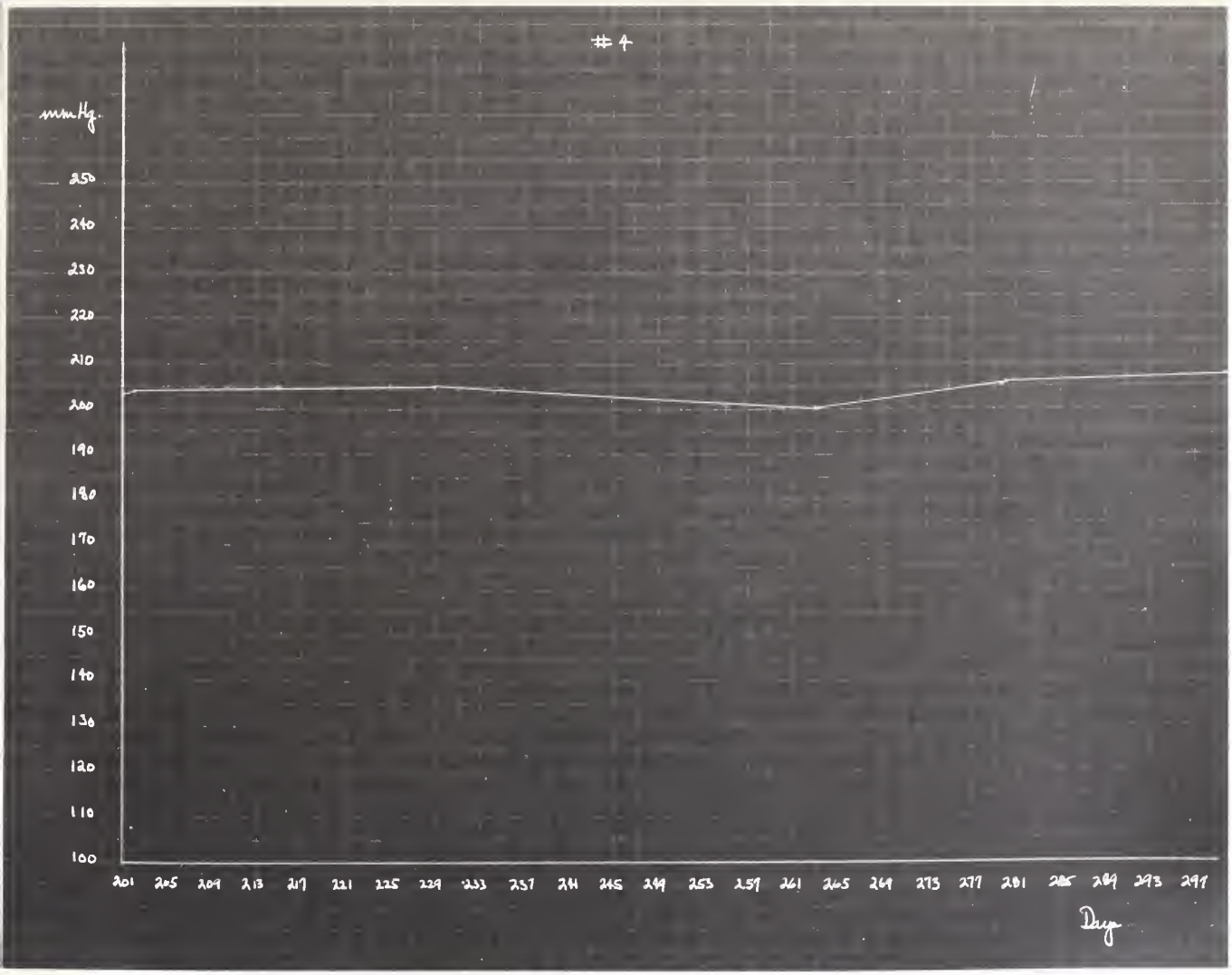
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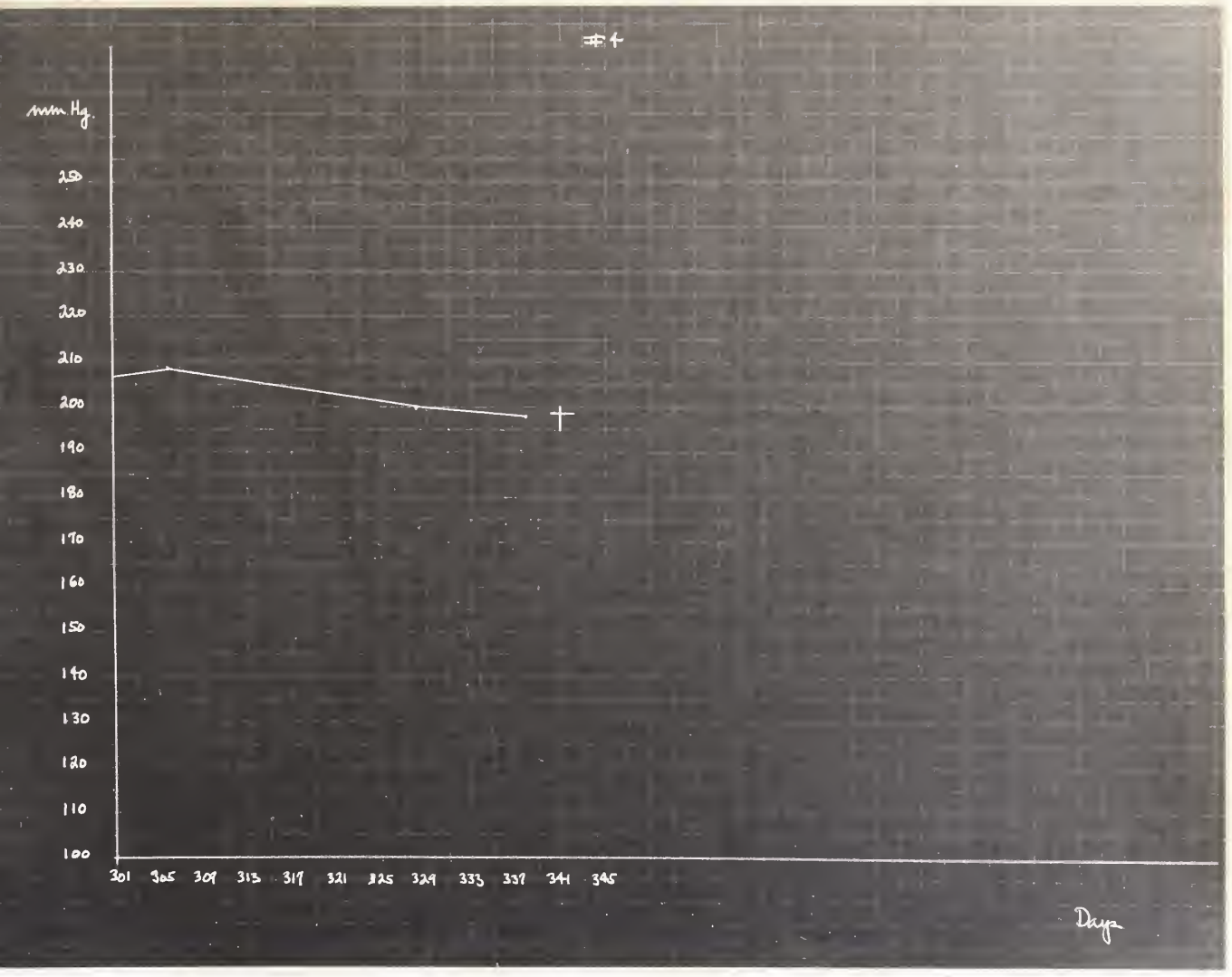
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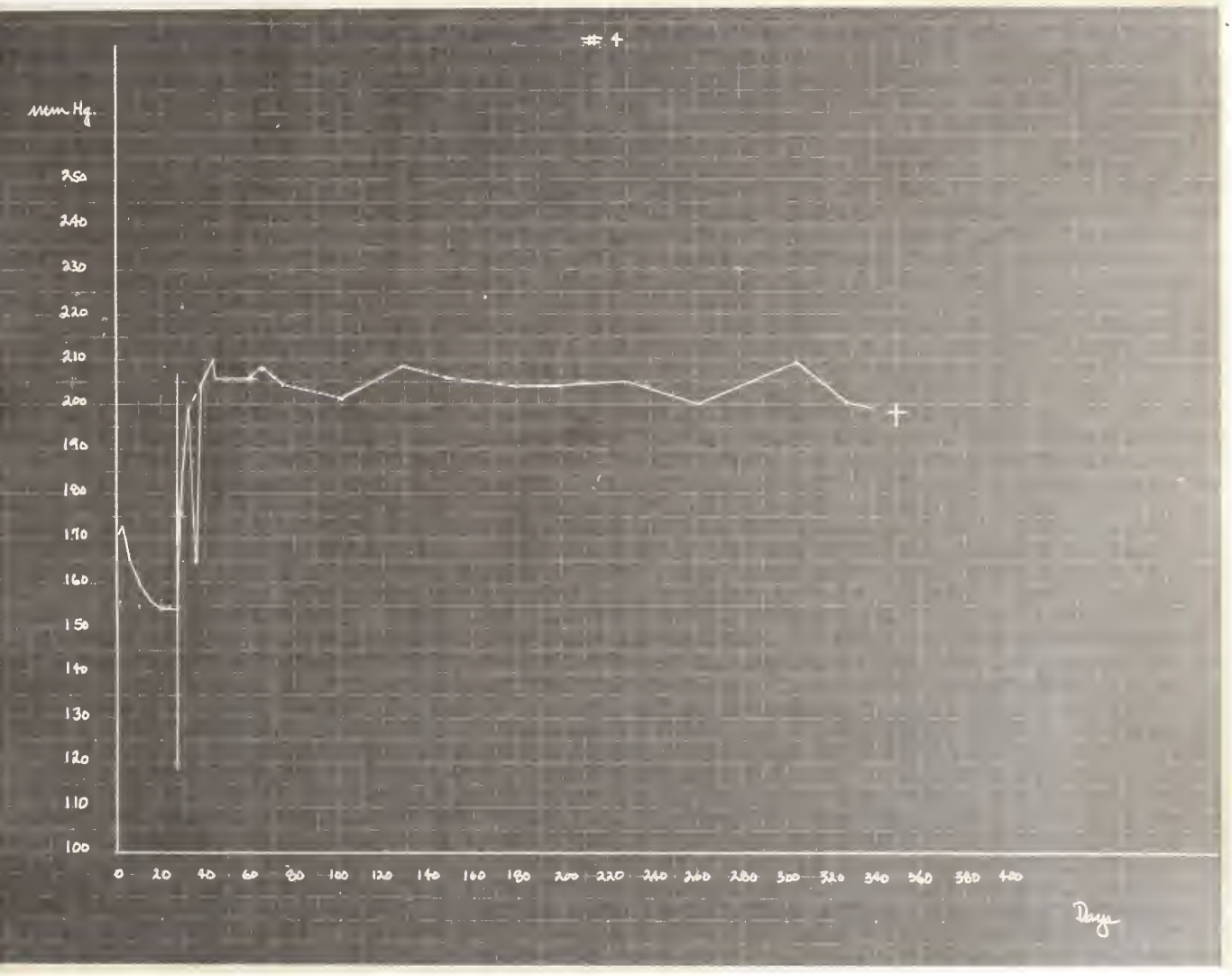
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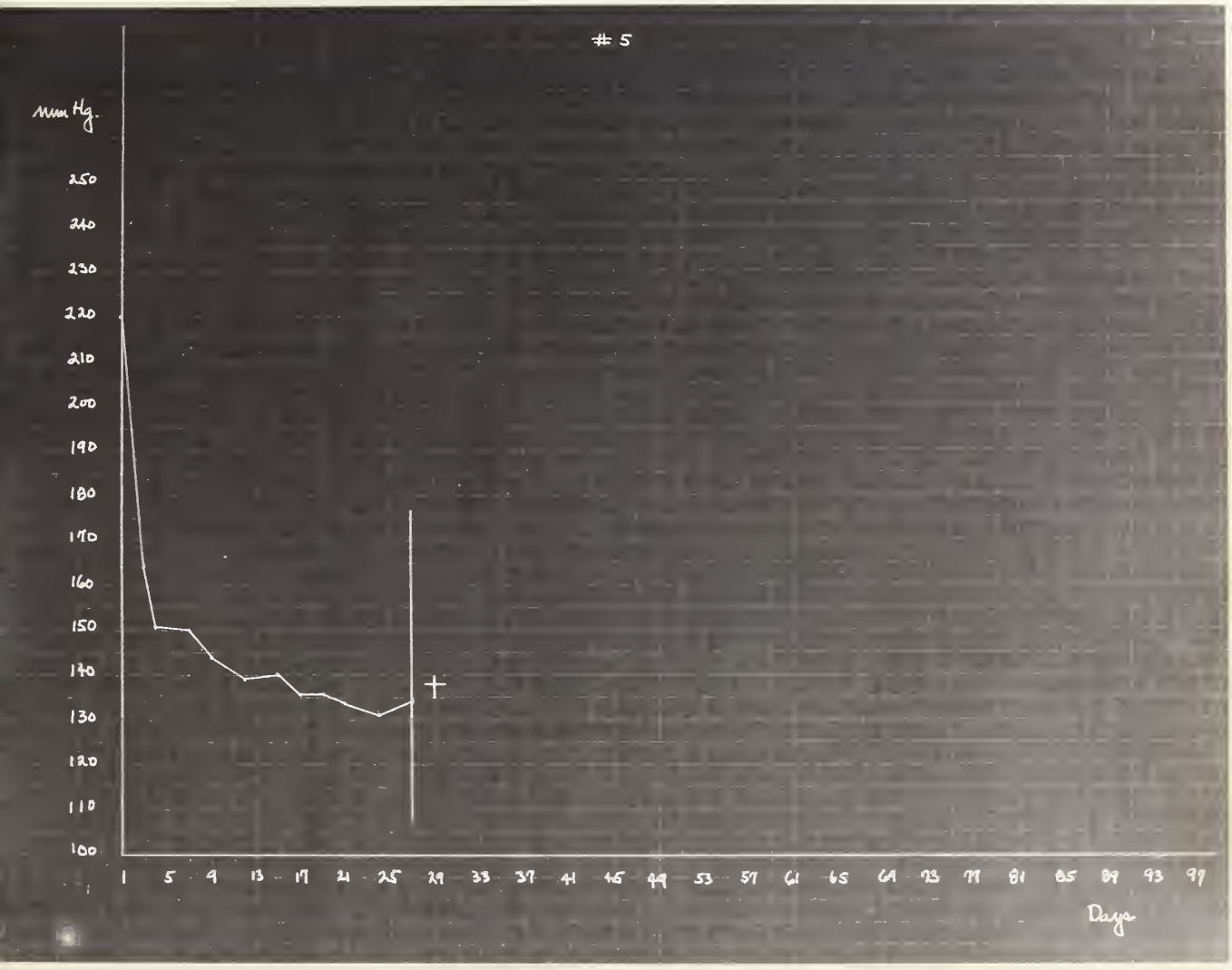
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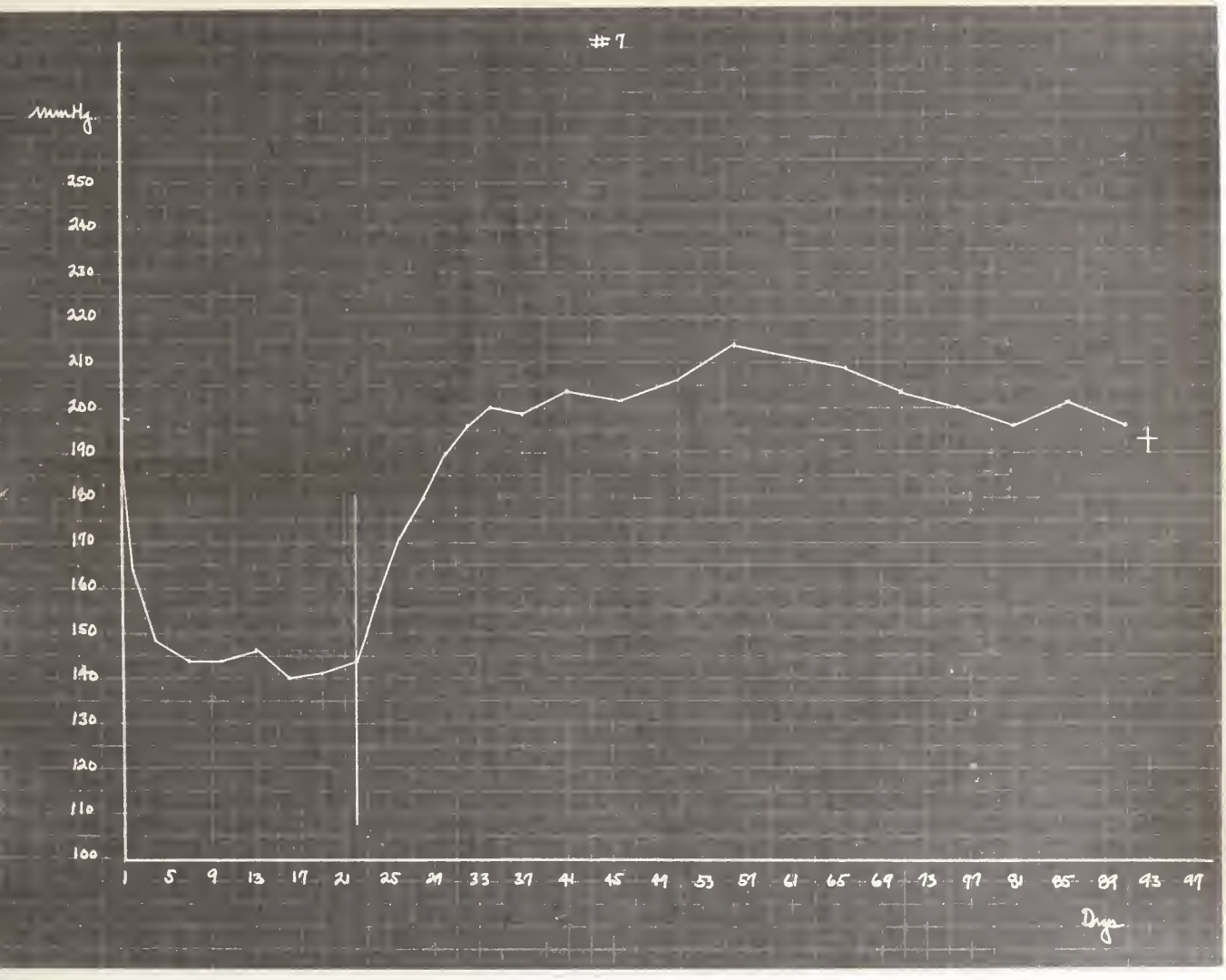
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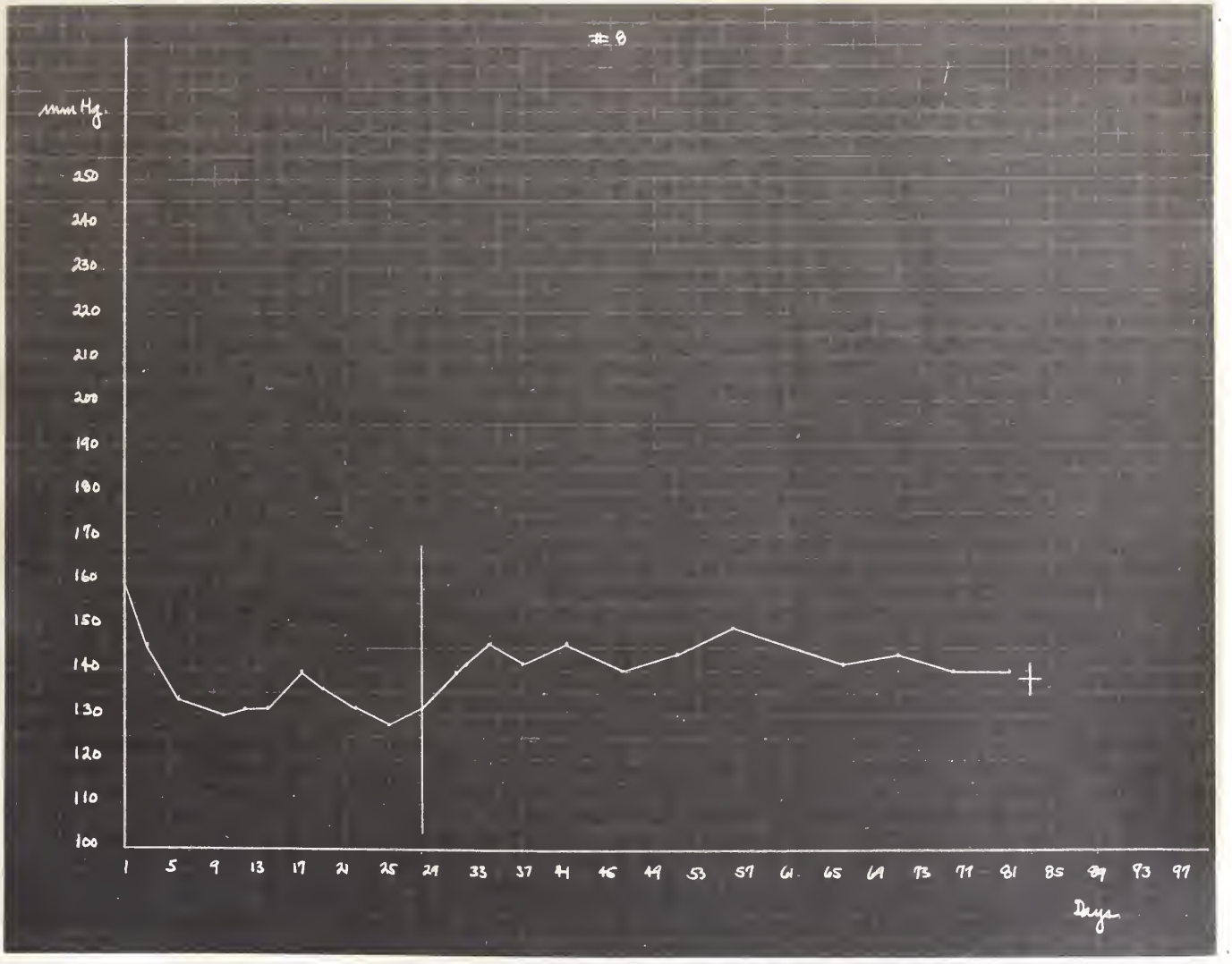
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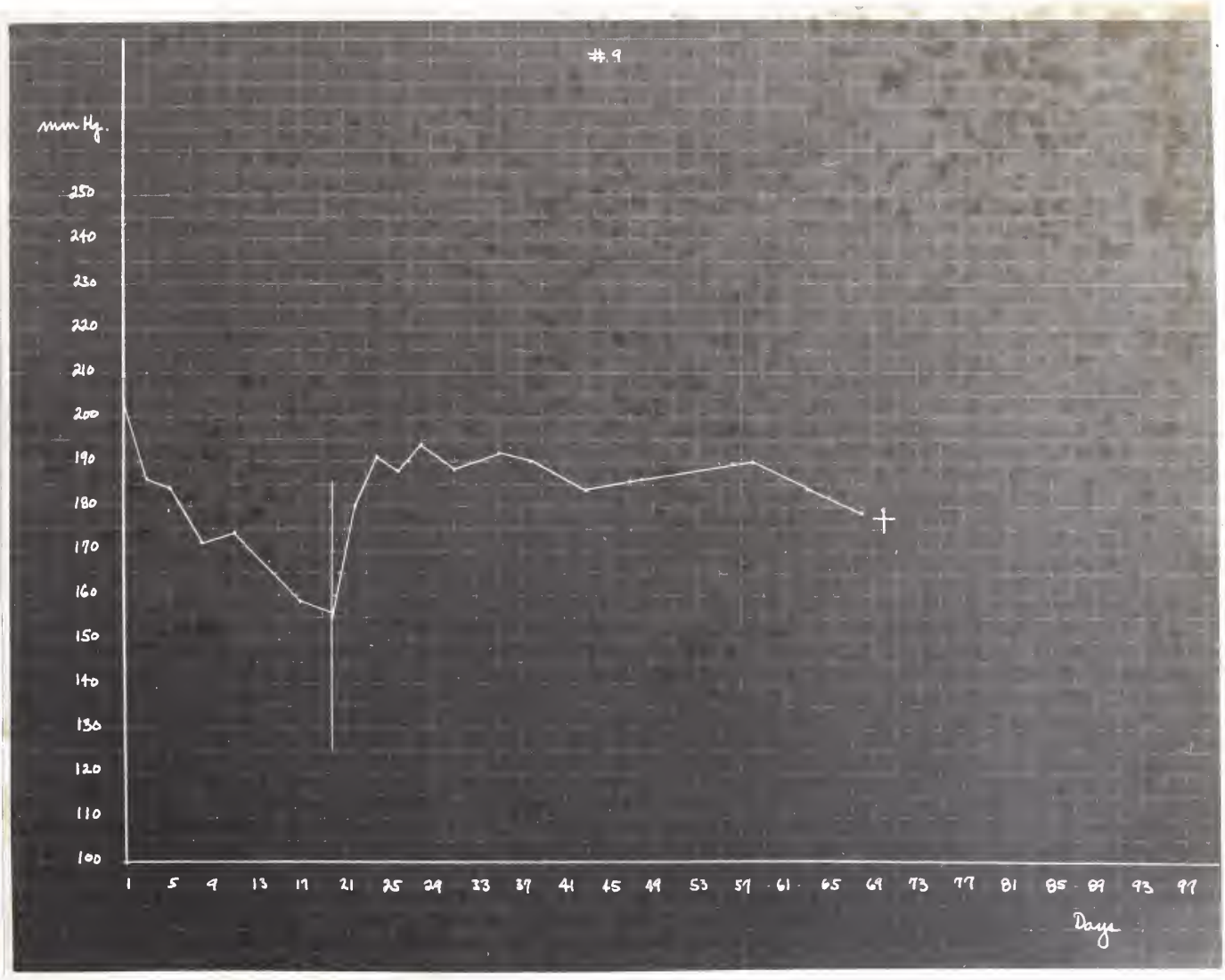
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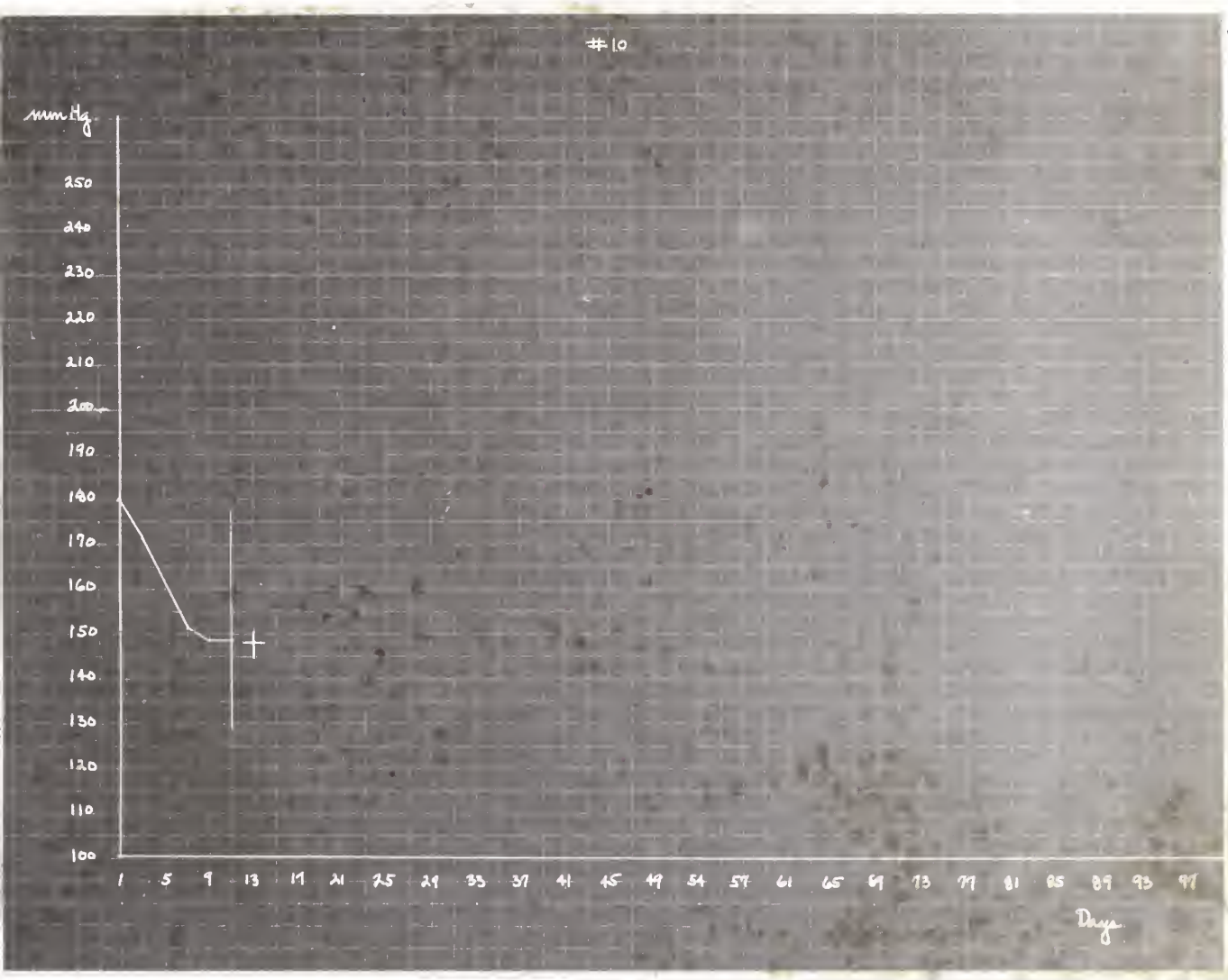
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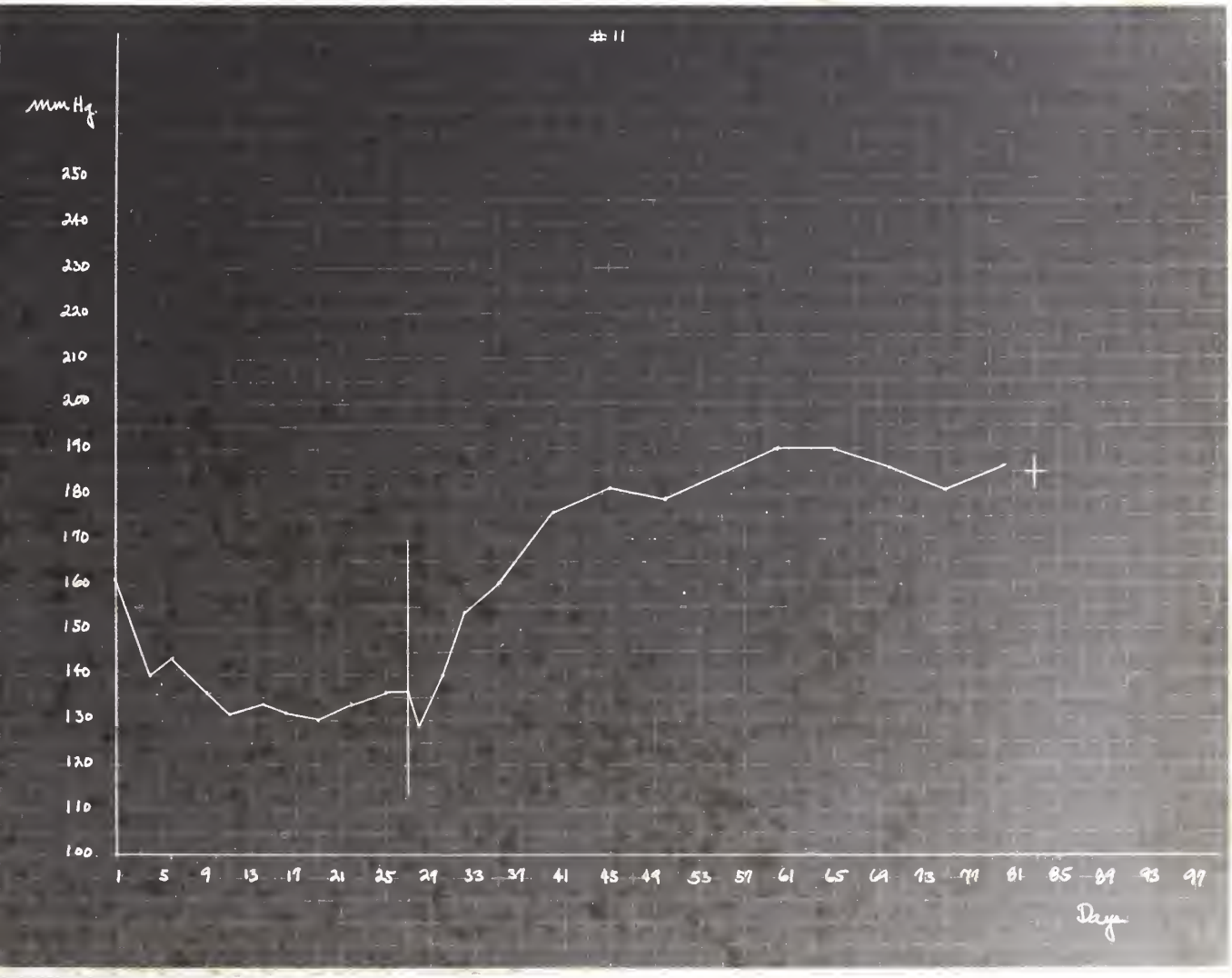
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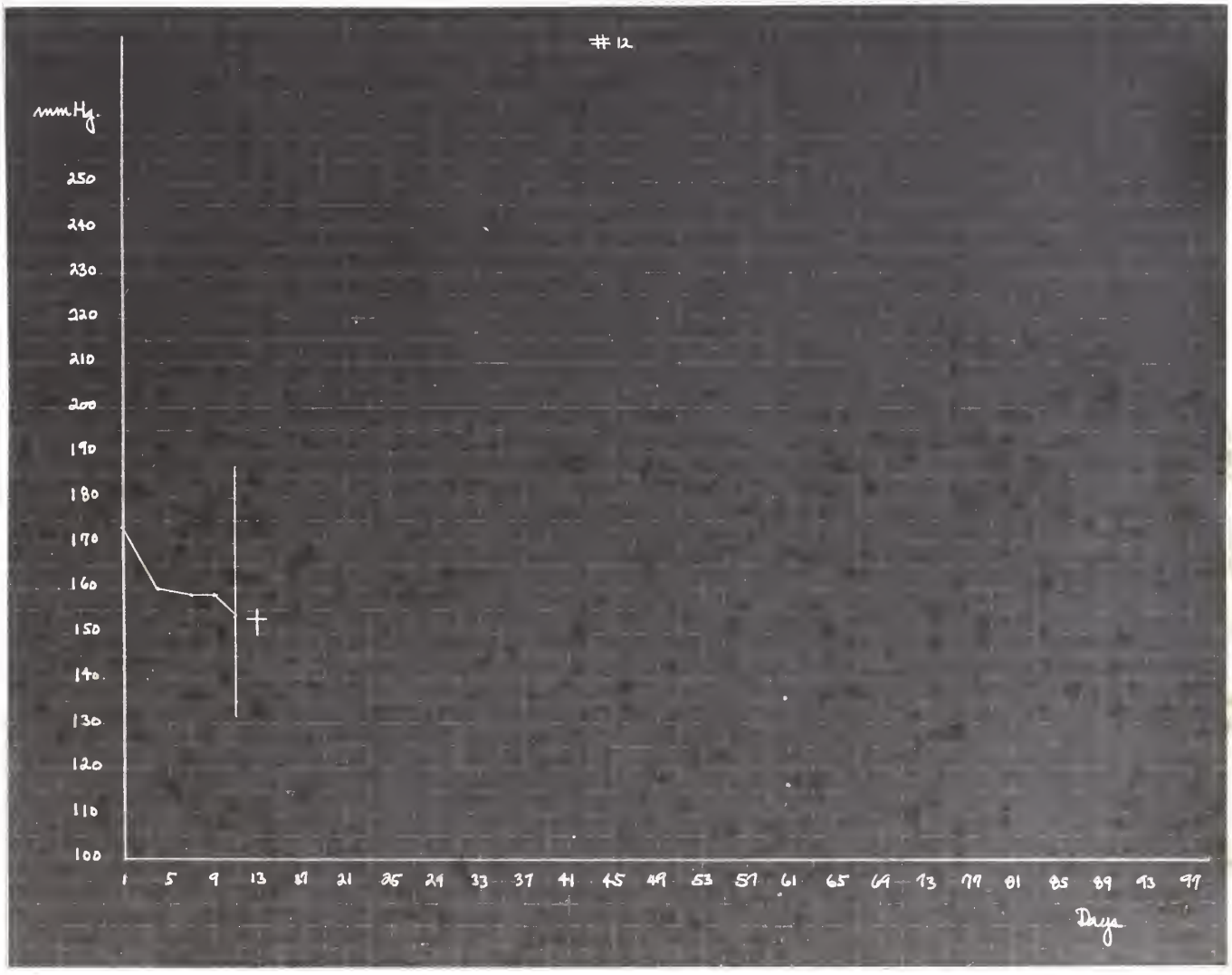
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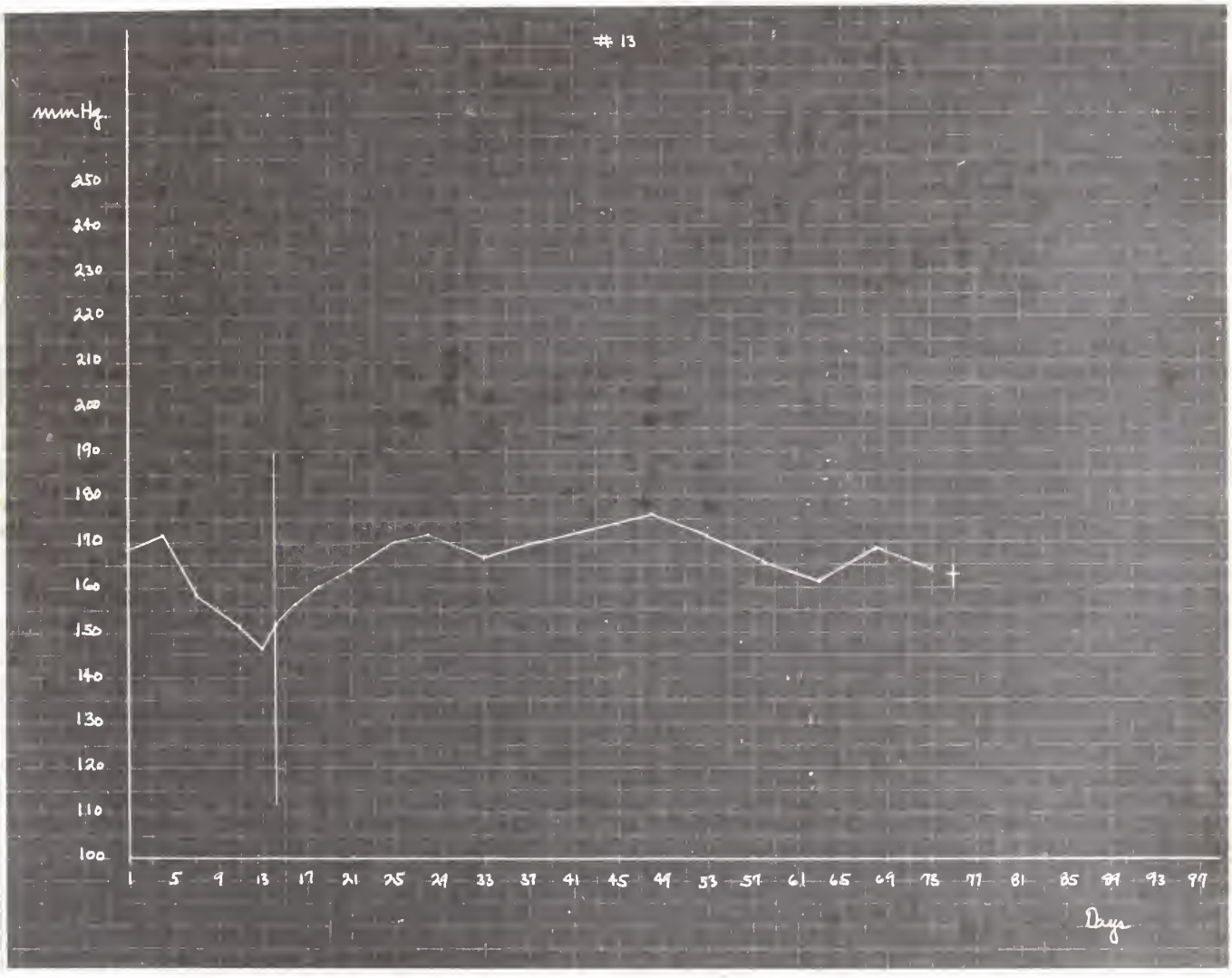
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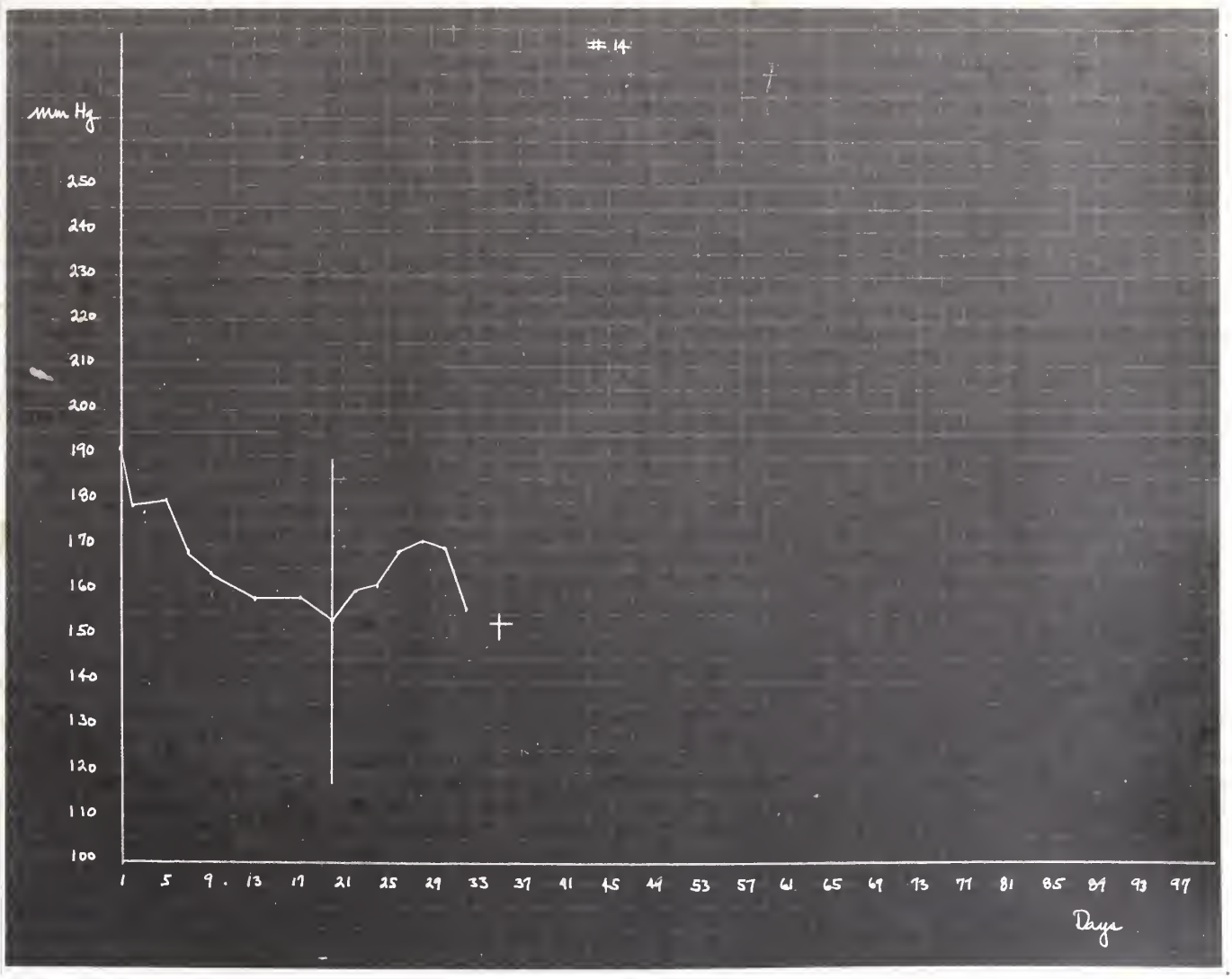
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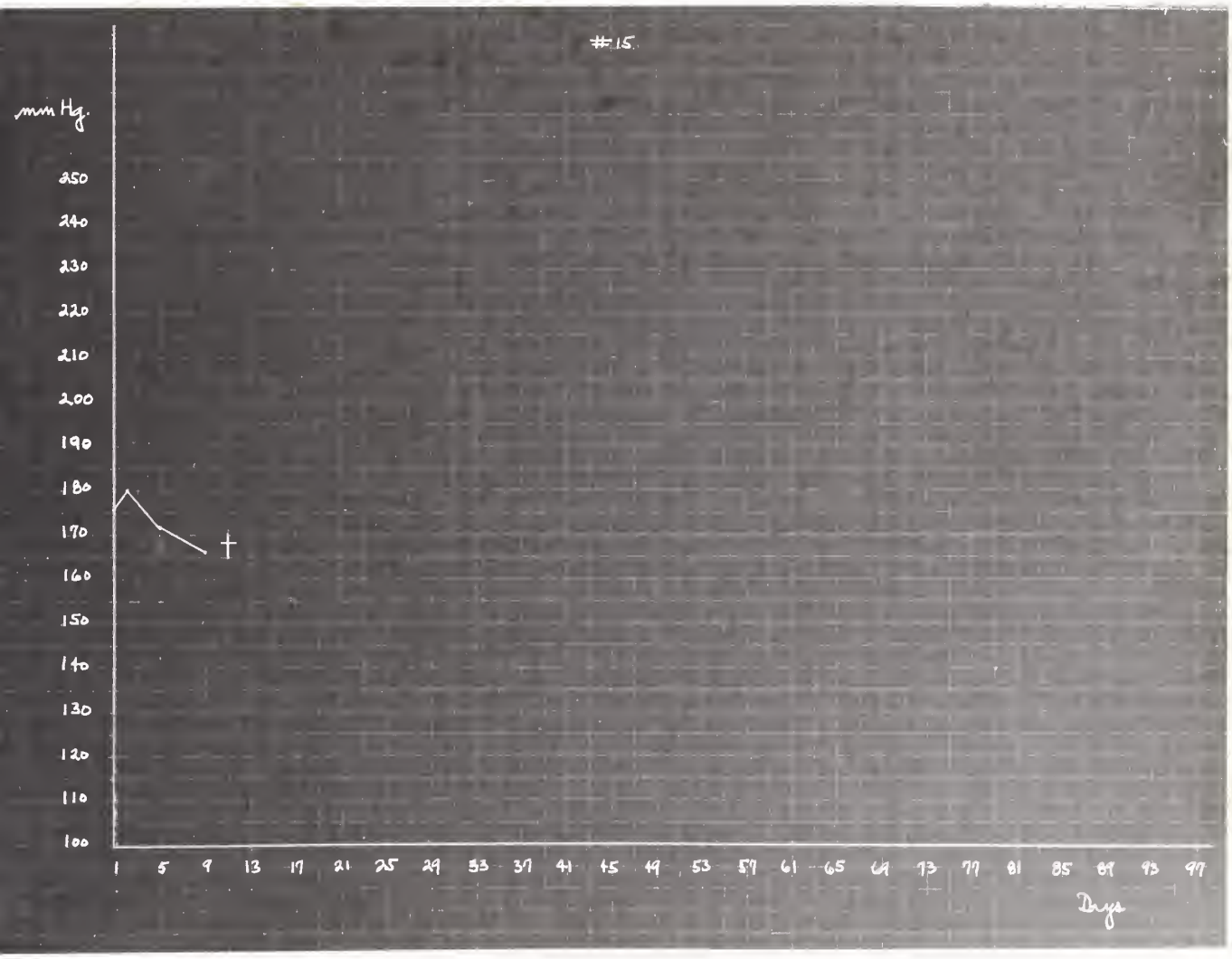
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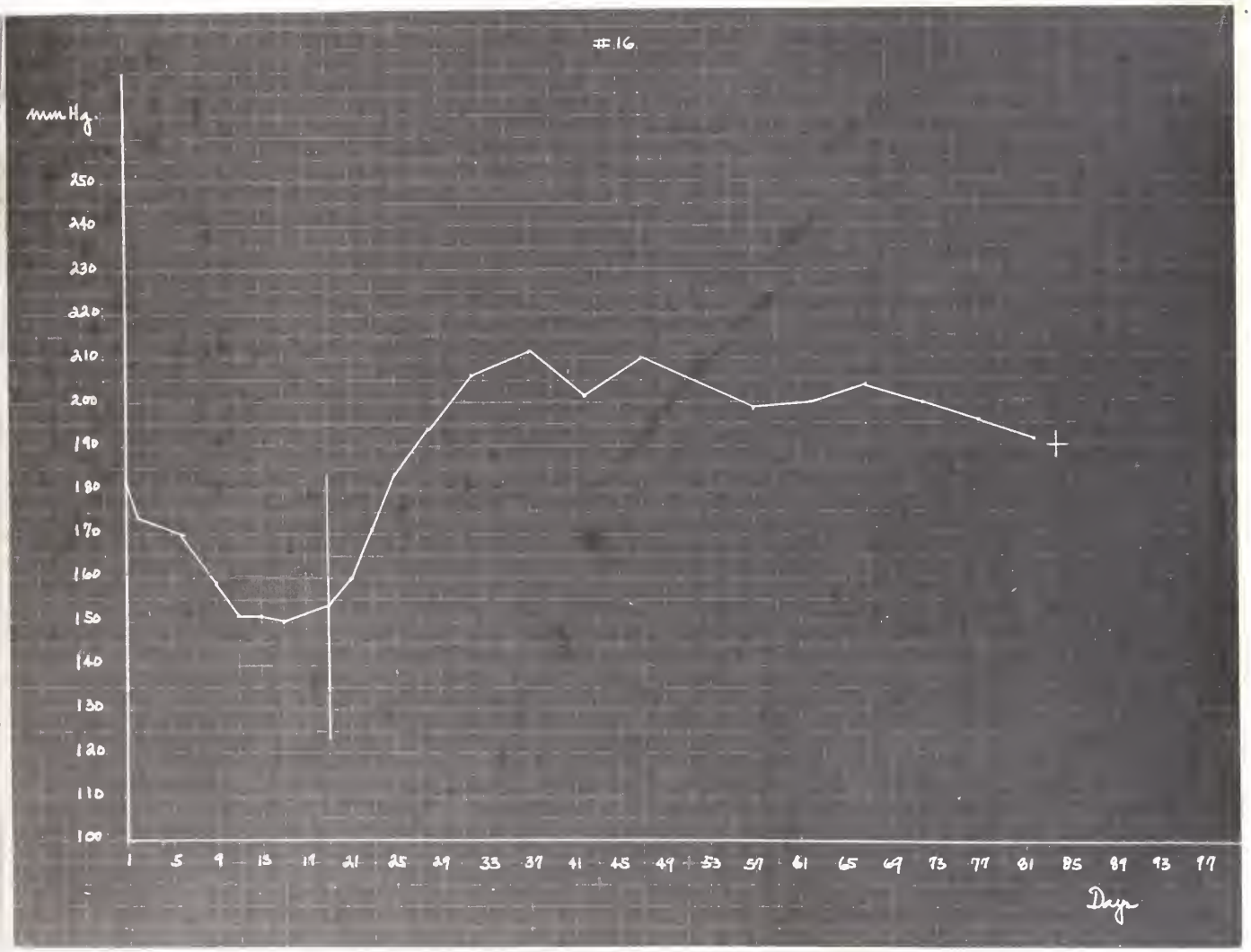
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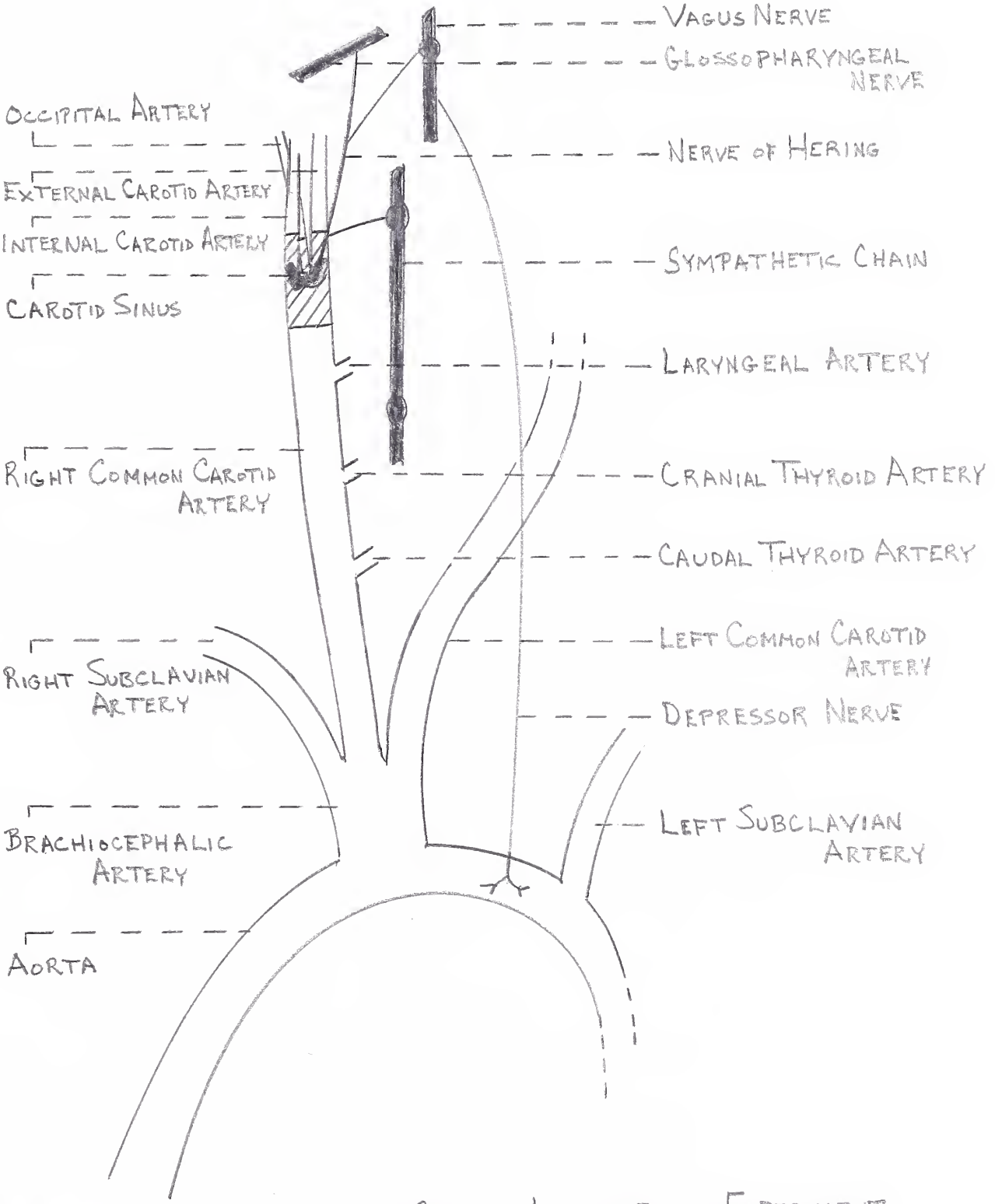


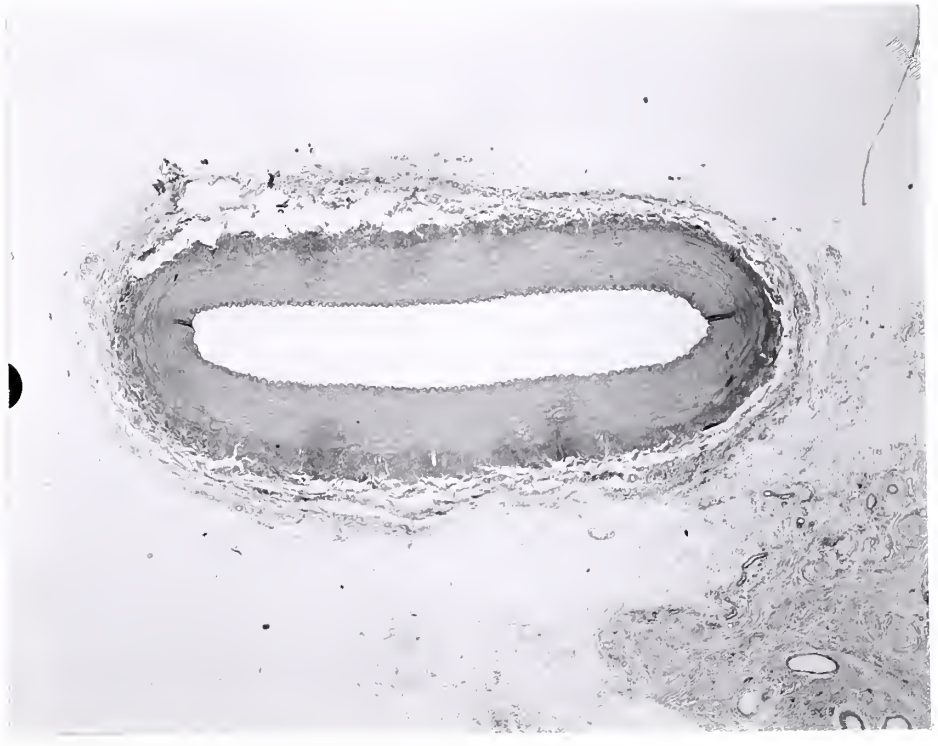
DIAGRAMMATIC SKETCH OF REGION INVOLVED IN EXPERIMENT
(DOG)

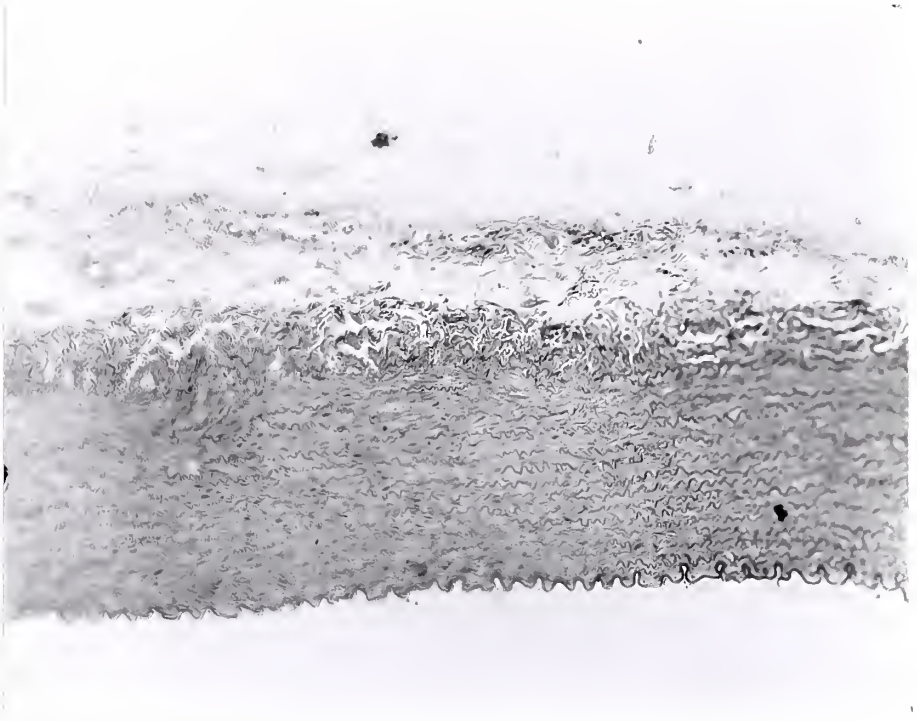
▨ = AREA COVERED WITH PLASTIC SOLUTION

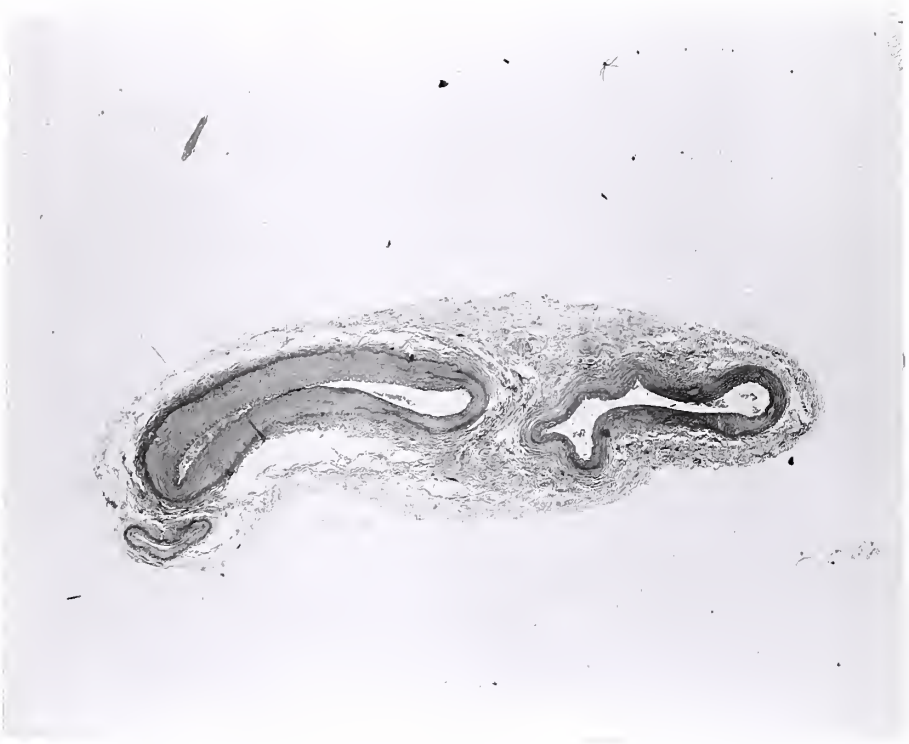
NOTE:

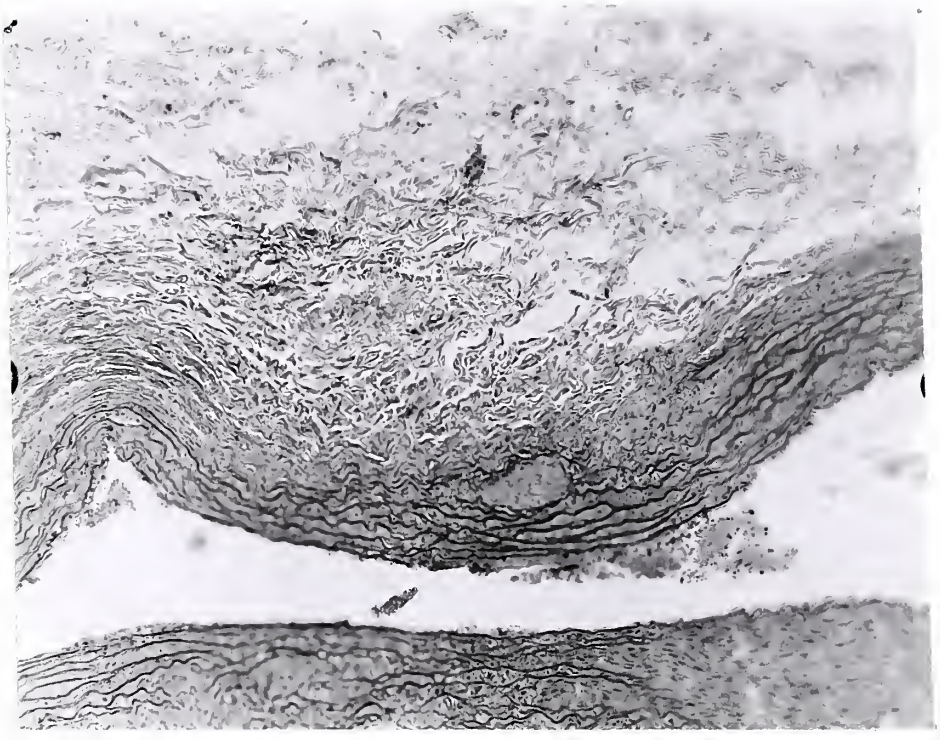
The four photomicrographs which follow are included to demonstrate difference in the periadventitial tissue (between a control (non-hypertensive) and an experimental (hypertensive) animal.)

Animal	Photomicrograph	Magnification
#8	A-1	X24
#8	A-2	X120
#4	B-1	X13
#4	B-2	X120









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